Niu *et al. Natural Products and Bioprospecting* 2023, **13**(1):3
https://doi.org/10.1007/s13659-022-00368-7

Natural Products and Bioprospecting

**REVIEW** **Open Access**

# The chemical structures and biological activities of indole diterpenoids

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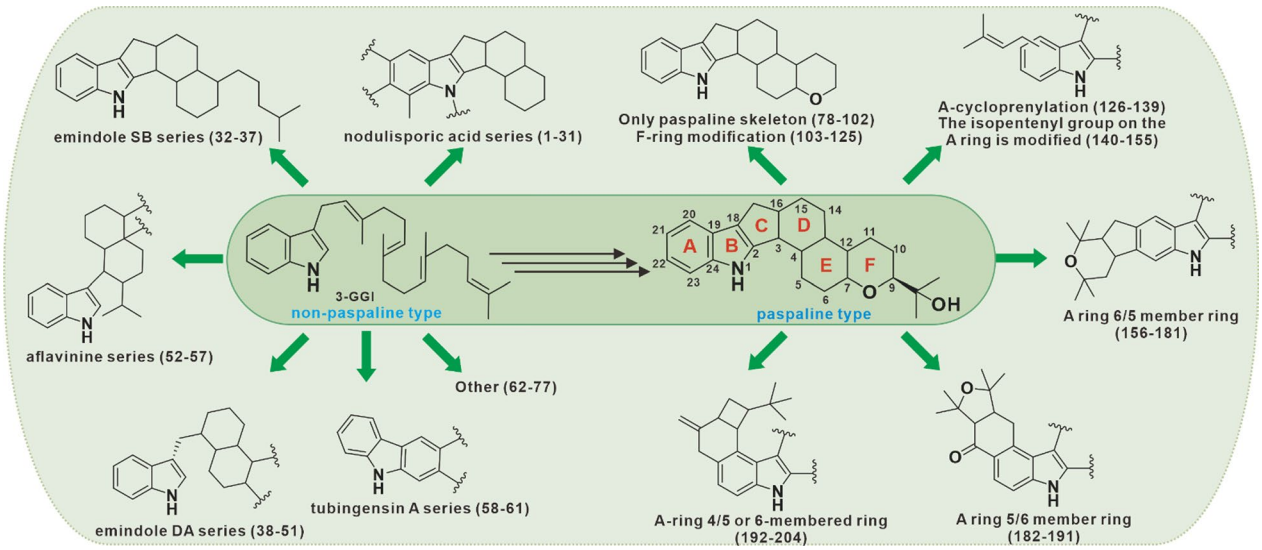
**Abstract**

Indole diterpenoids (IDTs) are an essential class of structurally diverse fungal secondary metabolites, that generally appear to be restricted to a limited number of fungi, such as *Penicillium*, *Aspergillus*, *Claviceps*, and *Epichloe* species, etc. These compounds share a typical core structure consisting of a cyclic diterpene skeleton of geranylgeranyl diphosphate (GGPP) and an indole ring moiety derived from indole-3-glycerol phosphate (IGP). 3-geranylgeranylindole (3-GGI) is the common precursor of all IDTs. On this basis, it is modified by cyclization, oxidation, and prenylation to generate a large class of compounds with complex structures. These compounds exhibit antibacterial, anti-insect, and ion channel inhibitory activities. We summarized 204 compounds of IDTs discovered from various fungi over the past 50 years, these compounds were reclassified, and their biological activities were summarized. This review will help to understand the structural diversity of IDTs and provide help for their physiological activities.

**Keywords** Indole diterpenoids, Structural classification, Physiological activity, Fungus

**Graphical Abstract**

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## 1 Introduction

IDTs are a structurally diverse class of fungal secondary metabolites, all sharing a common core structure consisting of indole, and a diterpene carbon backbone derived from four mevalonate-derived isoprene units [1]. The molecular complexity of these compounds is achieved by adding more isoprene units to the core structure and by various modifications such as oxidation, cyclization, and halogenation. IDTs are ubiquitous in the natural environment, and moldy food produced by *Penicillium* sp. is a common source of these compounds. For example, the fungus *P. tularense* found in tomatoes has metabolites such as janthitrems, paspalinine, paxilline, etc. [2]. *P. crustosum*, which produces the shivering mycotoxin penitrems, is a common foodborne fungus that can cause the spoilage of many foods [3].

Most of the IDTs are potent tremor mammalian mycotoxins [4], that also exhibit excellent biological activities, including cytotoxic, antibacterial, antiviral, and protein tyrosine phosphatase inhibitory activities [5]. To date, some IDT compounds have been used for drug discovery. For example, as BK channel blockers, IDTs have been shown to reduce intraocular pressure and have been used to treat glaucoma [6]. The H1N1 virus is an invasive strain of influenza virus that can cause death in humans, and many IDTs have also shown significant activity against the H1N1 virus, especially emndole SB [7]. In agricultural settings, there has been a general trend toward using tremor-free IDTs as pesticides, such as 20,25-dihydroxyaflavinine [8].

According to previous reports, 3-GGI is a common precursor compound of all IDTs. The origin of the indole ring in its structure was clarified in 1983, when Jesus et al. studied the biosynthesis of penitrem A, the results of isotope labeling experiments showed that the indole part was derived from the IGP precursor of tryptophan[9]. In 2013, Tagami et al. analyzed a pentenyltransfer PaxC in paxilline biosynthetic gene cluster, and proved that indole ring derived from IGP through in vitro enzyme activity experiment [10]. Next, on this basis, IDT can be further divided into two types, namely the paspaline type with a large proportion and a small part of the non-paspaline type. There are some reviews related to IDTs have been presented. For example, the synthesis and activity of paspaline-type compounds [11, 12], the structural diversity and biological activity [5], biosynthesis of IDTs are described [13–15]. However, considering that these reviews do not classify these two types of compounds uniformly, and exclude the cover of the latest IDT compounds in recent years. So here, we renamed the IDT skeleton rings **A**, **B**, **C**, **D**, **E**, and **F**, and 77 non-paspaline skeleton and 127 paspaline skeleton IDTs were uniformly reclassified and summarized according to their structures and oxidative modifications. This review will contribute to the scientific community's comprehensive and compact understanding of the complex and diverse IDTs.

## 2 Non-paspaline skeleton type

### 2.1 Nodulisporic acid series

A significant feature of this series is a caproic acid attached to the **E** ring, which contains 31 kinds of IDT compounds (Fig. 1 and Table 1). Nodulisporic acid A (NsA A, **1**) was discovered in *Hypoxylon pulicicidum* in 1992, and was first reported as a potent insecticide in 1997 [16]. It exhibits optimal activity with an LD90 (lethal dose 90%) of 1.5 μM in the flea assay and an $IC_{50}$ (half maximal inhibitory concentration) of 0.00027 μM in the binding assay [17]. In 1999, Otto D et al. found the compounds nodulisporic acid A1 (NsA A1, **2**) and nodulisporic acid A2 (NsA A2, **3**) from *Nodulisporium* spp., the LD50 (lethal dose 50%) of **2** to green flies was 0.3–1 μg/mL, like compound **1**. In the mosquito larvae assay, compound **2** was the strongest with an LD90 of 200 ng/mL [18], while **3** was slightly less active, with an LD50 of 0.6–1.5 μg/mL [19]. From *Nodulisporium* spp., nodulisporic acid B (NsA B, **4**), nodulisporic acid B1 (NsA B1, **5**), nodulisporic acid B2 (NsA B2, **6**), dehydro-NsA B (**7**), dehydro-NsA C (**8**) and derivative-compound **9–12** were found in 2002, in which **4** was 100 fold less active on fleas than **1**. **5** is slightly more active than **6**. It was also found that while the methyl ester derivative of **11** was tenfold less active than the corresponding acid **1**, the activity of **5** and its methyl ester **10** was similar. **10** might be slightly more potent than **4**. However, compounds **5**, **6**, and **12** were inactive at 100 ppm (parts per million) [20]. In 2003, nodulisporic acid C (NsA C, **13**), nodulisporic acid C1 (NsA C1, **14**), nodulisporic acid C2 (NsA C2, **15**) were found. **13** showed good activity against fleas, which was 10 times lower than **1**, and the LD90 was 10 μg/ml; but compounds **14** and **15** had no activity in the flea test. The activity of compound **13** was significantly lower in mosquito larvae and fly maggot larvae assays (LD90 = 10,000 ng/mL) [21]. In 2004, nodulisporic acid D (NsA D, **16**), D1 (NsA D1, **17**), D2 (NsA D2, **18**), D3 (NsA D3, **19**), E (NsA E, **20**), F (NsA F, **21**), A4 (NsA A4, **22**) and compound **23–29** were successively discovered in the mutant strain *Nodulisporium* spp. In the flea assay test, compounds **16**, **20**, and **21** were 62, 12, and 30 fold less active than **1**, respectively. Nodulisporic acid containing a dienoic acid chain showed better activity in its series. For example, **1** is more active than **2** and **3**. However, in the NsA D series, the biological activity of **18** is significantly better than that of **16** and **17**. No biological activity was detected for compounds **23–29**, and$\Delta^{23 \text{ or } 24}$-nodulisporic acids (**27**,

**28**, **29**) were less active than corresponding nodulisporic acids of the same class [18]. In 2022, Zhang YH et al. isolated two specific compounds, oxalerpene A and B (**30** and **31**), from *Penicillium oxalicum*. **30** is the first IDT derivative with a 4-hydroxy-5,5-dimethylhydrofuran-3-one in the five-membered side chain. **31** has a unique 6/5/6/6/6/6/6/5/5/5 ring system. Oxalerpene A and B have antiviral activity against H1N1 and respiratory syncytial virus (RSV) with $IC_{50}$ values from 2.8 to 9.4 μM [22].

## 2.2 Emindole SB series

The emindole SB series is different from the Nodulisporic acid series in that there is no caproic acid on the E ring (Fig. 2 and Table 2). In 1966, the compound emindole SB (**32**) was isolated from *Claviceps paspali*, which was cytotoxic to cancer cell lines, and also showed antibacterial activity against *Staphylococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC 6633 [23–25]. In 2010, asporyzin C (**33**) was isolated from *Aspergillus oryzae*, and the antibacterial activity against *E. coli* as well as the antifungal

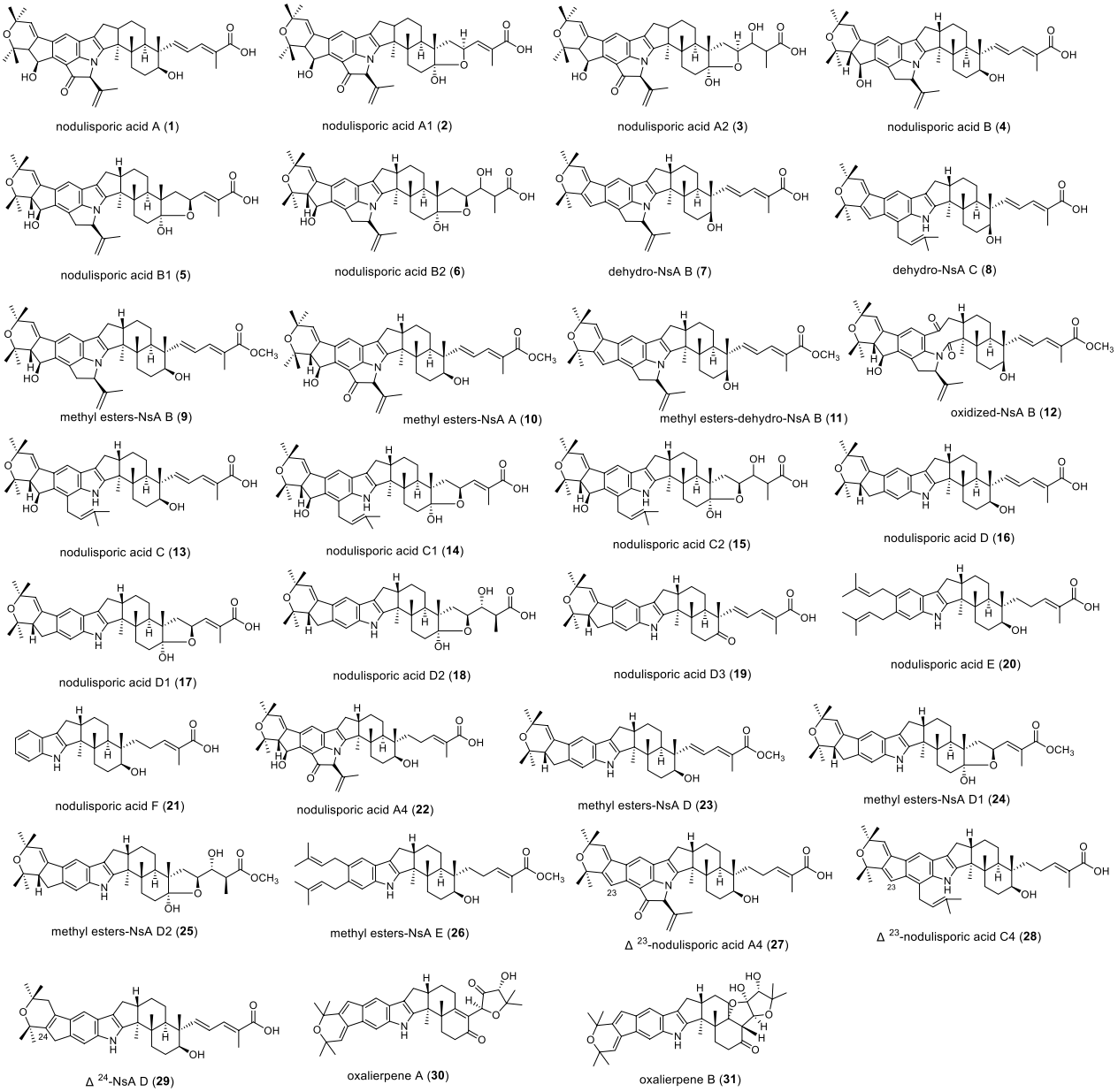



**Fig. 1** Chemical structures of nodulisporic acid series

**Table 1** Name, bioactivities and source of nodulisporic acid series

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **1** | Nodulisporic acid A | Insecticidal activity | *H. pulicicidum* | [16] |
| **2** | Nodulisporic acid A1 | Insecticidal activity | *Nodulisporium* spp. | [19] |
| **3** | Nodulisporic acid A2 | Insecticidal activity | *Nodulisporium* spp. | [19] |
| **4** | Nodulisporic acid B | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **5** | Nodulisporic acid B1 | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **6** | Nodulisporic acid B2 | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **7** | Dehydro-NsA B | | *Nodulisporium* spp. | [17] |
| **8** | Dehydro-NsA C | | *Nodulisporium* spp. | [17] |
| **9** | Methyl esters-NsA B | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **10** | Methyl esters-NsA A | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **11** | Methyl esters-dehydro-NsA B | Less active | *Nodulisporium* spp. | [20] |
| **12** | Oxidized-NsA B | Insecticidal activity | *Nodulisporium* spp. | [20] |
| **13** | Nodulisporic acid C | Flea agent | *Nodulisporium* spp. | [21] |
| **14** | Nodulisporic acid C1 | | *Nodulisporium* spp. | [21] |
| **15** | Nodulisporic acid C2 | | *Nodulisporium* spp. | [21] |
| **16** | Nodulisporic acid D | Flea agent | *Nodulisporium* spp. | [18] |
| **17** | Nodulisporic acid D1 | Flea agent | *Nodulisporium* spp. | [18] |
| **18** | Nodulisporic acid D2 | Flea agent | *Nodulisporium* spp. | [18] |
| **19** | Nodulisporic acid D3 | | *Nodulisporium* spp. | [18] |
| **20** | Nodulisporic acid E | Insecticidal activity | *Nodulisporium* spp. | [18] |
| **21** | Nodulisporic acid F | Flea agent | *Nodulisporium* spp. | [18] |
| **22** | Nodulisporic acid A4 | Insecticidal activity | *Nodulisporium* spp. | [18] |
| **23** | Methyl esters-NsA D | | *Nodulisporium* spp. | [18] |
| **24** | Methyl esters-NsA D1 | | *Nodulisporium* spp. | [18] |
| **25** | Methyl esters-NsA D2 | | *Nodulisporium* spp. | [18] |
| **26** | Methyl esters-NsA E | | *Nodulisporium* spp. | [18] |
| **27** | $\Delta^{23}$-NsA A4 | Less active | *Nodulisporium* spp. | [18] |
| **28** | $\Delta^{23}$-NsA C4 | Less active | *Nodulisporium* spp. | [18] |
| **29** | $\Delta^{24}$-NsA D | | *Nodulisporium* spp. | [18] |
| **30** | Oxalierpene A | Antiviral | *P.oxalicum* | [22] |
| **31** | Oxalierpene B | Antiviral | *P.oxalicum* | [22] |

activity against plant pathogens *Colletotrichum lagenarium* and *Fusarium oxysporium* were assayed. **33** exhibited intense activity against *E. coli* with an inhibitory diameter of 8.3 mm [25]. In 2020, the natural product penerpene J (**34**) was found in the fungus *Penicillium* sp. KFD28. This compound has inhibitory activity against both PTP1B (protein tyrosine phosphatase 1B) and TCPTP (protein tyrosine phosphatase), with $IC_{50}$ values of 9.5 μM and 14.7 μM, respectively [26]. In 2021, Chaiyosang B et al. isolated three novel IDTs aculeatupenes A-C (**35**–**37**) from the mycelium of *Aspergillus aculeatus* KKU-CT2. Compounds **35** and **36** showed weak cytotoxicity against HelaS3, KB, HepG2, MCF-7, and A549 cancer cell lines with $IC_{50}$ values of 11.12–67.81 μM. **37** showed weak cytotoxicity against the HelaS3 cell line with an $IC_{50}$ value of 17.48 μM, but no cytotoxicity against the vero cell line. Moreover, it was also found to exhibit weak antifungal activity against *Bacillus cereus* [27].

### 2.3 Emindole DA series

The common feature of this series of compounds is that they contain a 6/6-membered ring linked to a methylene group at the 3-position of the indole ring (Fig. 3 and Table 3). In 1988, the X-ray molecular structures of emindole DA (**38**) and DB (**39**) from *Emericella desertorum* were reported, both of which are tremor toxic to mammals [28, 29]. In 1989, nominine (**40**) was isolated as the leading organic soluble component of the sclerotium of the fungus *Aspergillus nomius* NRRL 13,137, which showed potent activity against the widespread crop pest *Heliothis zea*. When added to the standard test diet at 100 ppm dry weight, it resulted in 40% mortality and 97% weight loss relative to controls [30]. In 1992, compounds

radarin A–D (**41**–**44**) were isolated from the fungus *Aspergillus sulphureus*. When added to a standard test diet of the corn worm *Helicoverpa zea* at 100 ppm, **41** reduced body weight gain by 52.7% relative to the control after 1 week. **43** also showed some activity at the same concentration, resulting in a 17.1% reduction in body weight gain. While **42** and **44** were inactive. Further biological evaluations were then performed to show that **41** was active against human lung cancer A549, breast cancer MCF7, and colon adenocarcinoma HT-29 cells with $ED_{50}$ values of 2.5, 5.5, and 1.9 μg/mL, respectively. **42** was active in all three cell lines with $ED_{50}$ (median effective dose) values of 2.0, 2.0,and 0.7 μg/mL, respectively [31]. In 1992, emeniveol (**45**) was isolated from *Emericella nivea*, and when the concentration was 100 mg/L, it could inhibit the germination of pine pollen and the growth of camellia pollen by about 35.5% [32]. In 2006, three IDTs were isolated from the mycelium of *Emericella purpurea*, namely emindoles PA (**46**), PB (**47**), and PC (**48**), among which **47** has strong anti-cancer activity [33]. Later, it found that its precursor compound preemindole PA (**49**) [13]. Liu L et al. isolated the compound penicindopene A (**50**) from *Penicillium* sp. YPCMAC1 in 2019, that showed moderate cytotoxicity to A549 and HeLa cell lines, with $IC_{50}$ values of 15.2 and 20.5 μM, respectively [34]. In 2021, the compound penerpenes M (**51**) was discovered from the fungus *Penicillium* sp. KFD28. However, no antibacterial activity was found [35].

### 2.4 Aflavinine series

This series difference from the emindole DA series is that the 3-position of the indole ring is directly connected with the 6/6-membered ring (Fig. 4 and Table 4). In 1988, aflavinine (**52**) and its natural derivative products 20,25-dihydroxyaflavinine (**53**), 14-hydroxyflavinine (**54**), 24,25-dihydro-10,11-dihydro-20-hydroxyflavinine (**55**) and 10,11-dihydro-11,12-dihydro-20-hydroxyflavinine (**56**) were isolated from the fungus *Aspergillus flavus*, and these metabolites were selectively distributed to the sclerotia, It also showed antifeedant activity to fungus eating insects that usually encounter sclerotia in nature [8]. Compound **52** was non-toxic and non-tremor to 1-day-old chickens at 300 mg/kg. Compounds **54**–**56** were inactive against *C. hemipterus* at 100 ppm, but showed significant feeding deterrence when tested at the levels found in the sclerotia (400–1100 ppm). Compounds **53** and **54**–**56** also showed mild activity against *Bacillus subtilis* in a standard disk assay of 100 mg/disk, but were not toxic to brine shrimp at 250 mg/ml [36]. In 2019, Han X et al.

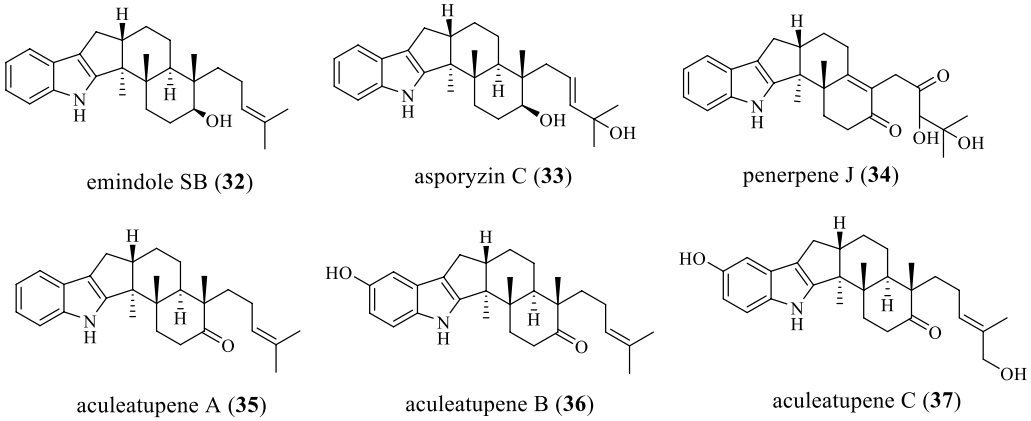



**Fig. 2** Chemical structures of emindole SB series

**Table 2** Name, bioactivities and source of emindole SB series

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **32** | Emindole SB | Anti-cancer, antibacterial | *C. paspali* | [24] |
| **33** | Asporyzin C | Antibacterial | *A. oryzae* | [25] |
| **34** | Penerpene J | Anti-cancer | *Penicillium* sp.KFD28 | [26] |
| **35** | Aculeatupene A | Anti-cancer | *A. aculeatus* KKU-CT2 | [27] |
| **36** | Aculeatupene B | Anti-cancer | *A. aculeatus* KKU-CT2 | [27] |
| **37** | Aculeatupene C | Anti-cancer | *A. aculeatus* KKU-CT2 | [27] |

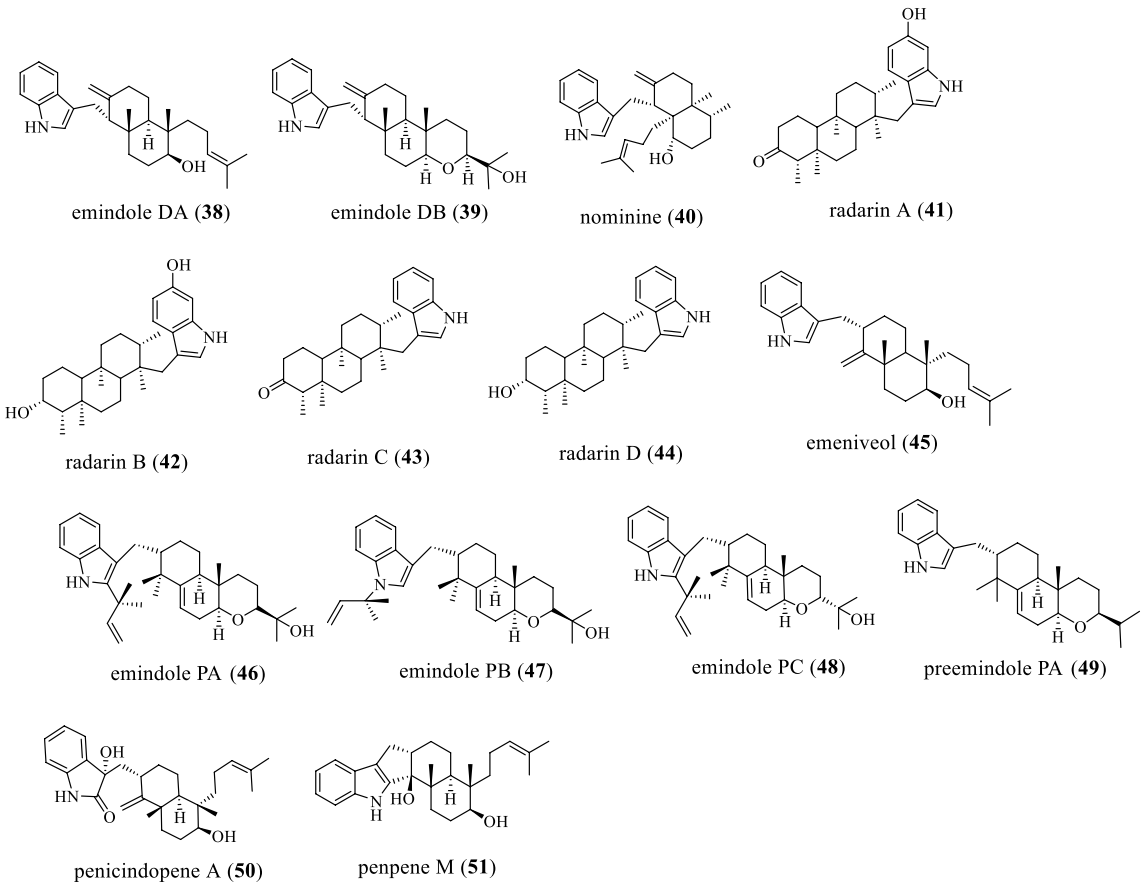



**Fig. 3** Chemical structures of emindole DA series

**Table 3** Name, bioactivities and source of emindole DA series

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **38** | Emindole DA | Tremor toxin | *E. desertorum* | [28] |
| **39** | Emindole DB | Tremor toxin | *E. desertorum* | [28] |
| **40** | Nominine | Insect resistance | *A. nomius* | [30] |
| **41** | Radarin A | Insect resistance | *A. sulphureus* | [31] |
| **42** | Radarin B | Insect resistance | *A. sulphureus* | [31] |
| **43** | Radarin C | Insect resistance | *A. sulphureus* | [31] |
| **44** | Radarin D | Insect resistance | *A. sulphureus* | [31] |
| **45** | Emeniveol | Pollen growth inhibitor | *E. nivea* | [32] |
| **46** | Emindole PA | | *E. purpurea* | [33] |
| **47** | Emindole PB | Anti-cancer | *E. purpurea* | [33] |
| **48** | Emindole PC | | *E. purpurea* | [33] |
| **49** | Preemindole PA | | | [13] |
| **50** | Penicindopene A | cytotoxicity | *Penicillium* sp. | [34] |
| **51** | Penerpenes M | | *Penicillium* sp. | [35] |

isolated a new IDT cladosporine A (**57**) from the extract of the fungal strain *Cladosporium* sp. JNU17DTH12-9-01, which was the first report of the existence of IDT in *Cladosporium* spp. The MIC(minimum inhibitory concentration) of this compound to *Staphylococcus aureus* 209P and *Candida albicans* FIM 709 was 4 μg/mL and 16 μg/mL, respectively [37].

### 2.5 Tubingensin A series

The structure of this series is characterized by the presence of a benzene ring attached to the indole ring B (Fig. 5 and Table 5). In 1989, tubingensin A (**58**) and its structural isomer tubingensin B (**59**) were isolated from the fungus *Aspergillus tubingensis* by Gloer JB and colleagues, and **58** was found to be resistant to the general crop pest *Heliothis zea*, and exhibit showed in vitro antiviral activity against herpesvirus type I [38], while **59** showed mild activity against the crop pest *H. zea*, resulting in a 10% mortality rate when added to a standard diet at 125 ppm. The compound also showed almost identical activity to **58** in assays against herpes simplex virus type I with an $IC_{50}$ of 9 μg/mL, but was more cytotoxic to HeLa cells ($IC_{50}$ 4 μg/mL) [39]. In 1990, the compound aflavazole (**60**) was isolated from *Aspergillus flavus*. When added at 100 ppm to the standard test diet, **60** showed significant feeding-rejecting activity against the fungus-eating beetle *Carpophilus hemipterus* and was second only to dihydroxyaflavinine in activity against *C. hemipterus* among the IDT mycorrhizal metabolites of *A. flavus* [40]. When added to diets at concentrations found in *A. flavus* sclerotia (200–600 ppm), almost complete feeding deterrence was observed [40, 41]. In 2019, Miles CO and his colleagues isolated the compound shearilicine (**61**) from the strain *Penicillium* sp. ZO-R1-1, which had an $IC_{50}$ value of less than 10 μM against L5178Y or A2780 cells, was tested against the human embryonic kidney cell line HEK-293. The results showed the highest selectivity in tests with SI (selectivity index) values in the range 3.3–8.1 and were also the most active metabolite against L5178Y cells with an $IC_{50}$ value of 3.6 μM and A2780 cells with an $IC_{50}$ value of 8.7 μM [42].

### 2.6 Other non-paspaline skeleton type compounds

This series contain irregular non-paspaline type compounds (Fig. 6 and Table 6). In 1992, the compound paxinorol (**62**), isolated from the fungus *Penicillium paxilli*, which was found to be toxic to mammals, and it reduced the activity behavior of mice, but returned

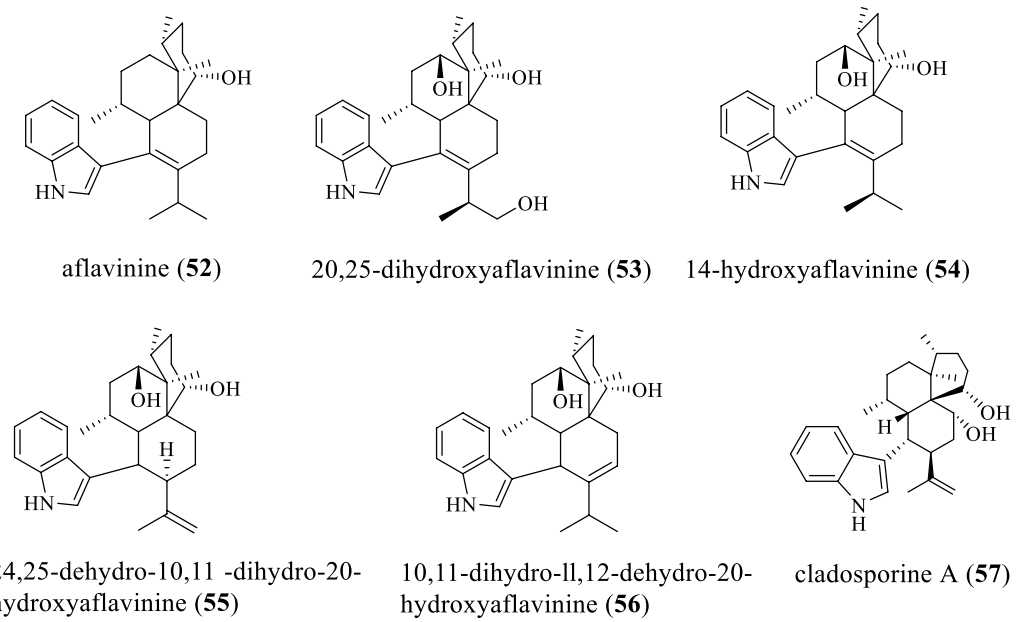
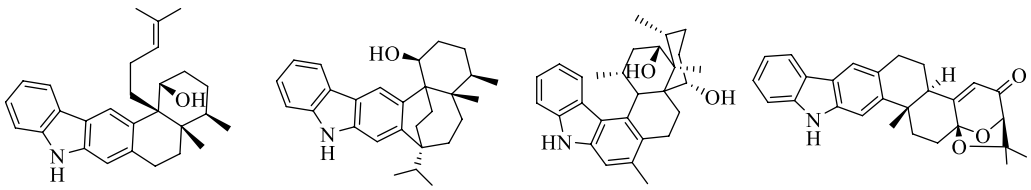



**Fig. 4** Chemical structures of aflavinine series

**Table 4** Name, bioactivities and source of aflavinine series

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **52** | Aflavinine | Insect resistance | *A. tubingensis* | [36] |
| **53** | 20,25-Dihydroxyaflavinine | Insect resistance | *A. flavus* | [8] |
| **54** | 14-Hydroxyaflavinine | Insect resistance | *A. flavus* | [8] |
| **55** | 24,25-Dehydro-10,11-dihydro-20-hydroxyaflavinine | Insect resistance | *A. flavus* | [8] |
| **56** | 10,ll-Dihydro-ll,12-dehydro-20-hydroxyaflavinine | Insect resistance | *A. flavus* | [8] |
| **57** | Cladosporine A | Antibacterial | *Cladosporium* sp. | [37] |

to normal after some time [43]. In the same year, the compound sulpinine C (**63**) was isolated from *Aspergillus sulphureus*, which was weakly active against *H. zea* but inactive against *C. hemipterus* [44]. In 1992, Gloer JB and his colleagues reported the anti-insect metabolite aspernomine (**64**) from *Aspergillus nomius*, which showed moderate activity against *H. zea*. Incorporating this compound at 100 ppm into the standard test diet resulted in a 35% reduction in body weight gain of the test insects relative to the control. Moreover, it also exhibited cytotoxicity against three human tumor cell lines, with $ED_{50}$ values of 3.09, 4.93, and 3.08 μg/mL against A-549 lung, MCF-7 breast,and HT-29 colon adenocarcinoma cell lines, respectively [45]. In 1997, petromindole (**65**) was isolated by Ooike M et al. from the soil fungus *Petromyces* [46]. In 2002, two anthelmintic IDTs, thiersinine A (**66**) and B (**67**), were isolated from an organic extract of *P. thiersii* NRRL 28,147, which showed effective activity against *S. frugiperda* when added to standard test grains at 100 ppm, with growth compared to the control rates were reduced by 83% and 84% respectively. However, they were inactive against both *Candida albicans* ATCC 90,029 and *Staphylococcus aureus* ATCC 29,213 in the standard assay at 200 μg/plate [47]. In 2010, the natural products asporyzin A (**68**) and B (**69**) were isolated from *Aspergillus oryzae*, where **68** and **69** had lower insecticidal activity than their precursor JBIR-03, and neither of them showed any antifungal activity [25]. In 2010, the IDT JBIR-03 (**70**) was isolated from the fungus *Dichotomyces cejpii var.*, which showed anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activity and was tested at 32 and 64 mg/ml, respectively. Inhibits the growth of gram-positive and gram-negative bacteria at a concentration of any cytotoxic activity [48]. In 2013, the compound (6S,7R,10E,14E)-16-(1H-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol (**71**) was isolated from an acid fungal strain *Penicillium camemberti* OUCMDZ-1492, which showed significant protection against H1N1 virus-induced cytopathic with $IC_{50}$ values of 34.1 μM, respectively [7]. In 2016, Gao SS et al. discovered the compound rhizovarin D (**72**) from Rhizomucor *Mucor irregularis* QEN-189, which represents the most complex member of IDT derivatives [49]. In 2018, Zhao JC et al. isolated a new 1(2), 2(18)-diseco IDT drechmerin H (**73**) from the fermentation broth of *Drechmeria* sp. This compound exhibits a significant agonistic effect on the pregnane X receptor (PXR) with an $EC_{50}$ (concentration for 50% of maximal effect) value of 134.91 ± 2.01 nM [50]. In 2019, the IDT tolypocladin H (**74**) was isolated from the strain *Tolypocladium* sp. XL115, the compound is active against the fungus *A. fragariae* with MIC values of 6.25–50 μg/mL; also active against all bacteria tested, the MIC value is 12.5–25 μg/mL, but no cytotoxicity [51]. In 2020, Nur EAA et al. isolated a new IDT terpendole N (**75**) from *Volutella citrinella* BF-0440, but no physiological activity was found [52]. In 2021, the compound penerpene N (**76**) was identified from the fungus *Penicillium* sp. KFD28, which represents a second paxilline-type IDT with a 1,3-dioxane ring, has a low cytotoxic effect on Hela cancer cell lines, and no antimicrobial activity was found [35]. In 2021, the compound ascandinine A (**77**) was isolated from the Antarctic sponge-derived fungus *Aspergillus candidus* HDN15-152, which has




tubingensin A (**58**) tubingensin B (**59**) aflavazole (**60**) shearilicine (**61**)

**Fig. 5** Chemical structures of tubingensin A series

**Table 5** Name, bioactivities and source of tubingensin A series

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **58** | Tubingensin A | Anti-insect, anti-virus | *A. tubingensis* | [38] |
| **59** | Tubingensin B | Cytotoxicity | *A. tubingensis* | [39] |
| **60** | Aflavazole | Anti-insect | *A. flavus* | [40] |
| **61** | Shearilicine | Cytotoxicity | *Penicillium* sp. | [42] |

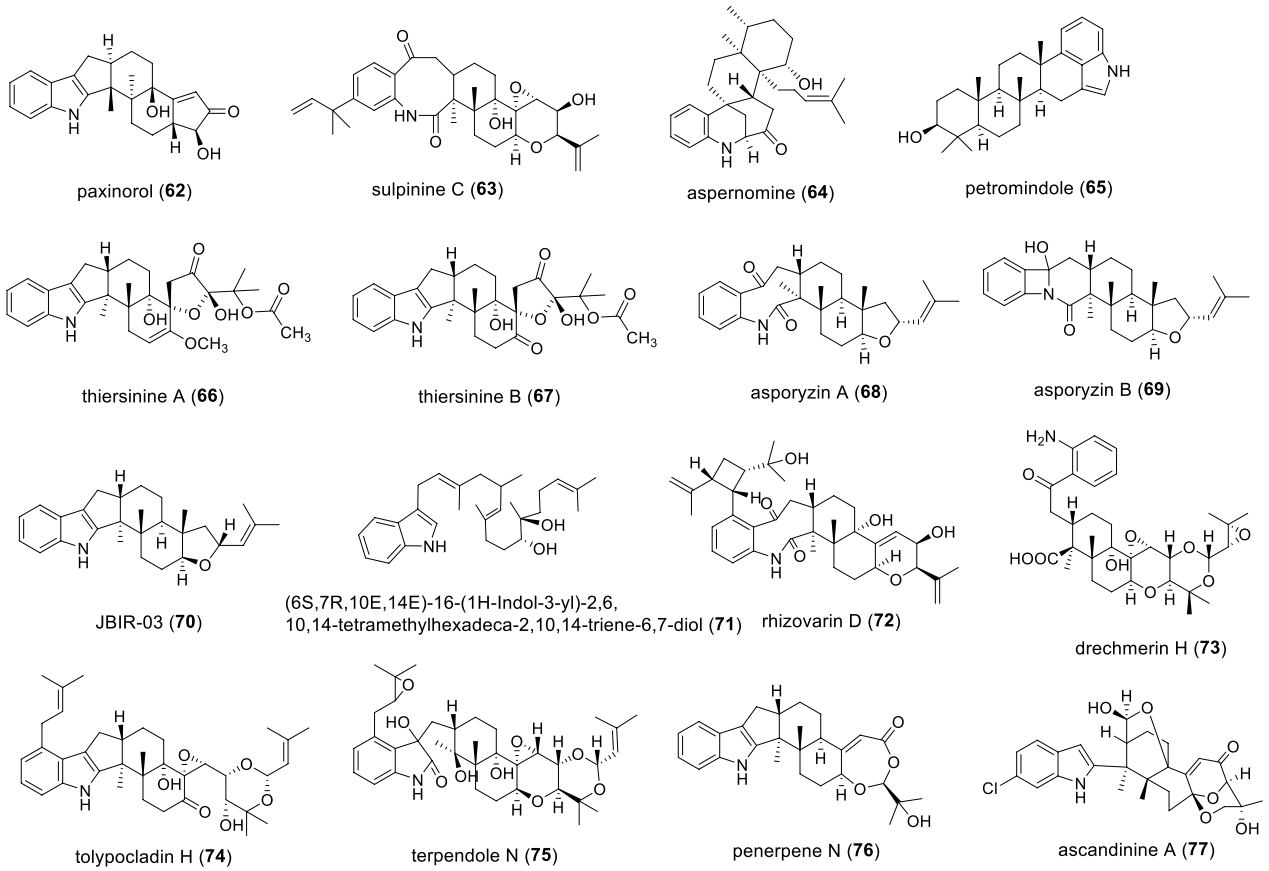



**Fig. 6** Chemical structures of other types of compounds

**Table 6** Name, bioactivities and source of other types of compounds

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **62** | Paxinorol | Animal toxicity | *P. paxilli* | [43] |
| **63** | Sulpinine C | Anti-insect | *Aspergillus sulphureus* | [44] |
| **64** | Aspernomine | Anti-insect, anti-cancer | *A. Nomius* | [45] |
| **65** | Petromindole | | *P. muricatus* | [46] |
| **66** | Thiersinine A | Anti-insect | *P. thiersii* | [47] |
| **67** | Thiersinine B | Anti-insect | *P. thiersii* | [47] |
| **68** | Asporyzin A | Insecticide | *A. oryzae* | [25] |
| **69** | Asporyzin B | Insecticide | *A. oryzae* | [25] |
| **70** | JBIR-03 | Anti-MRSA | *D. cejpii* | [48] |
| **71** | (6S,7R,10E,14E)-16-(1H-Indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol | Cytotoxicity | *P. camemberti* | [7] |
| **72** | Rhizovarin D | | *Mucor irregularis* | [49] |
| **73** | Drechmerin H | Agonistic effect on PXR | *Drechmeria* sp. | [50] |
| **74** | Tolypocladin H | Antibacterial activity | *Tolypocladium* sp. XL115 | [51] |
| **75** | Terpendole N | | *V. citrinella* BF-0440 | [52] |
| **76** | Penerpene N | Anti-cancer | *Penicillium* sp. | [35] |
| **77** | Ascandinine A | | *A.candidus* | [53] |

an unprecedented 2-oxabicyclo [2.2.2]octan-3-ol motif embedded in a pentacyclic system [53].

## 3 Paspaline skeleton type

### 3.1 Only paspaline skeleton

There are twenty-five IDT compounds containing only the paspaline skeleton (Fig. 7 and Table 7). In 1966, Arigoni D and his colleagues isolated the compound paspaline (**78**) from *Claviceps paspali*, which did not cause BK channel inhibition and tremor, but showed stronger anti-proliferative, anti-migratory, and Wnt/β-catenin inhibition than compound emindole SB [23, 54]. In the same year, Sarah et al. isolated the compound paspaline B (**79**) from the fungus *Penicilium paxilli*, which was the first oxidized analog of paspaline to be isolated, and also had tremor-causing activity for animals [55]. Paxilline (**80**) was first isolated from *P. paxilli* in 1974, and later Cole et al. reported that administration of 25 mg/kg of this compound caused severe intermittent tremors in roosters and mice [56, 57]. In 1989, Miles CO and colleagues discovered the compounds α-paxitriol (**81**) and β-paxitriol (**82**), neither of which caused tremors in mice [43]. In 1989, 1'-O-acetylpaxilline (**83**) was isolated from *Emericella striata*. When the injection concentration was 3.125 mg/kg, it could cause tremors in mice, and its tremor intensity was the same as that of paxilline. However, at the same time, it can also cause horn arch in mice [29]. In 1989, the compound 13-desoxypaxilline (**84**) was isolated from *Emericella* spp., which was active against human A-549 and HL-60 cancer cell lines, but had no antibacterial activity [35, 58]. In 1990, PC-M6 (**85**) was isolated from *P. crustosum*. The compound **85** showed moderate inhibitory activity against *Staphylococcus aureus* ATCC 6538, and also had activity for human gastric cancer cells [35, 59, 60]. In 1994, two compounds, 10β-hydroxy-13-desoxypaxilline (**86**) and 7α-hydroxy-13-desoxypaxilline (**87**), were isolated from the fungus *P. paxilli*, of which **86** showed significant resistance to human A-549 and HL-60 cancer cell lines, and it is the only paspaline-type IDTs that exhibits activity against both cell lines. **87** has tremor activity [61]. In 1995, Tomoda H et al. isolated and characterized terpendoles E (**88**), F (**89**), and G (**90**) from the culture broth of *Albophoma yamanashiensis* by using different production media [62]. They have a weak inhibitory effect on cholesterol acyltransferase (ACAT) activity, and **88** can be oxidatively modified to desoxyterpendole I (**123**) [63, 64]. In 1995, Belofsky et al. isolated the compound 7α-hydroxyl-13-dehydroxypaxilline (**91**) from *Eupenicillium Shearii* [65], which showed moderate inhibitory activity against *Staphylococcus aureus* ATCC 6538 and antibacterial activity against *Bacillus subtilis* ATCC 6633 (MIC = 16 μg/mL), but showed no inhibitory activity against *E. coli* ATCC 25,922 and *L. monocytogenes* ATCC 1911 [35]. In 2009, the compound penijanthine A (**92**) was isolated from the fungus *Penicillium janthinellum*, which had no antifungal activity against *Aspergillus fumigatus* IFM 41,362, *Aspergillus niger* IFM 41,398, *Candida albicans* ATCC 90,028 or *Cryptococcus neoformans* ATCC 90,112 [66]. In 2013, 4α-demethylpaspaline-4α-carboxylic-acid (**93**) and 4α-demethylpaspaline-3,4,4α-triol (**94**) were isolated from an acid fungal strain *Penicillium camemberti* OUC-MDZ-1492, and compound **94** was significant protection against H1N1 virus-induced cytopathic in MDCK cells with an $IC_{50}$ value of 32.2 μM [7]. In 2013, the IDTs 3-deoxo-4β-deoxypaxilline (**95**) and 2'-hydroxypaxilline (**96**) were isolated from an acid fungal strain *Penicillium camemberti* OUCMDZ-1492, and compound **95** exhibited significant protection against H1N1 virus-induced cytopathic with $IC_{50}$ value of 28.3 μM [7]. In 2014, the IDT 4β-deoxypenijanthine A (**97**) was isolated from the soil fungus *Penicillium* sp. CM-7, which showed no activity against human A-549 and HL-60 cancer cell lines [67]. In 2014, the IDT 4β-deoxy-1'-O-acetylpaxilline (**98**) was isolated from the soil fungus *Penicillium* sp. CM-7, which showed no effect on human A-549 and HL-60 cancer cell lines [67]. In 2019, during chemical research on the endophyte *Penicillium* sp. ZO-R1-1 was isolated from the medicinal plant ginger root, and the compounds 7-hydroxypaxilline-13-ene (**99**) and 7-methoxypaxilline (**100**) were discovered. Compound **99** showed cytotoxicity with $IC_{50}$ values in the range of 5.3–8.1 μM [42]. In 2021, the IDT penerpene K (**101**) was isolated from a fermentation broth produced by adding L-tryptophan to the medium of the fungus *Penicillium* sp. KFD28. It has inhibitory activity against PTP1B and TCPTP, but has no antibacterial activity and cytotoxicity [35]. In 2021, the compound epi-paxilline (**102**) was isolated from the marine-derived fungus *Penicillium* sp., which has inhibitory activity against PTP1B with $IC_{50}$ values of 31.5 μM, respectively [26, 35].

### 3.2 F-ring modification

Based on the paspaline skeleton, its **F**-ring was modified by epoxidation (Fig. 8 and Table 8). In 1966, Arigoni D and his colleagues isolated the compound paspalicine (**103**) from *Claviceps paspali*, a dehydroxylated analog of paspalinine lacking tremor activity [23]. It can effectively block maxi-K (high-conductance $Ca^{2+}$-activated $K^{+}$) channels [24, 54]. In 1980, Gallagher RT et al. discovered the compound paspalinine (**104**) from *Claviceps paspali*, a mycotoxin that causes tremors in mice [68]. In 1993, compounds 14-hydroxypaspalinine (**105**) and 14-(N, N-dimethylvalyloxy)-paspalinine (**106**) were isolated from the fungus *Aspergillus nomius*. At 100 ppm

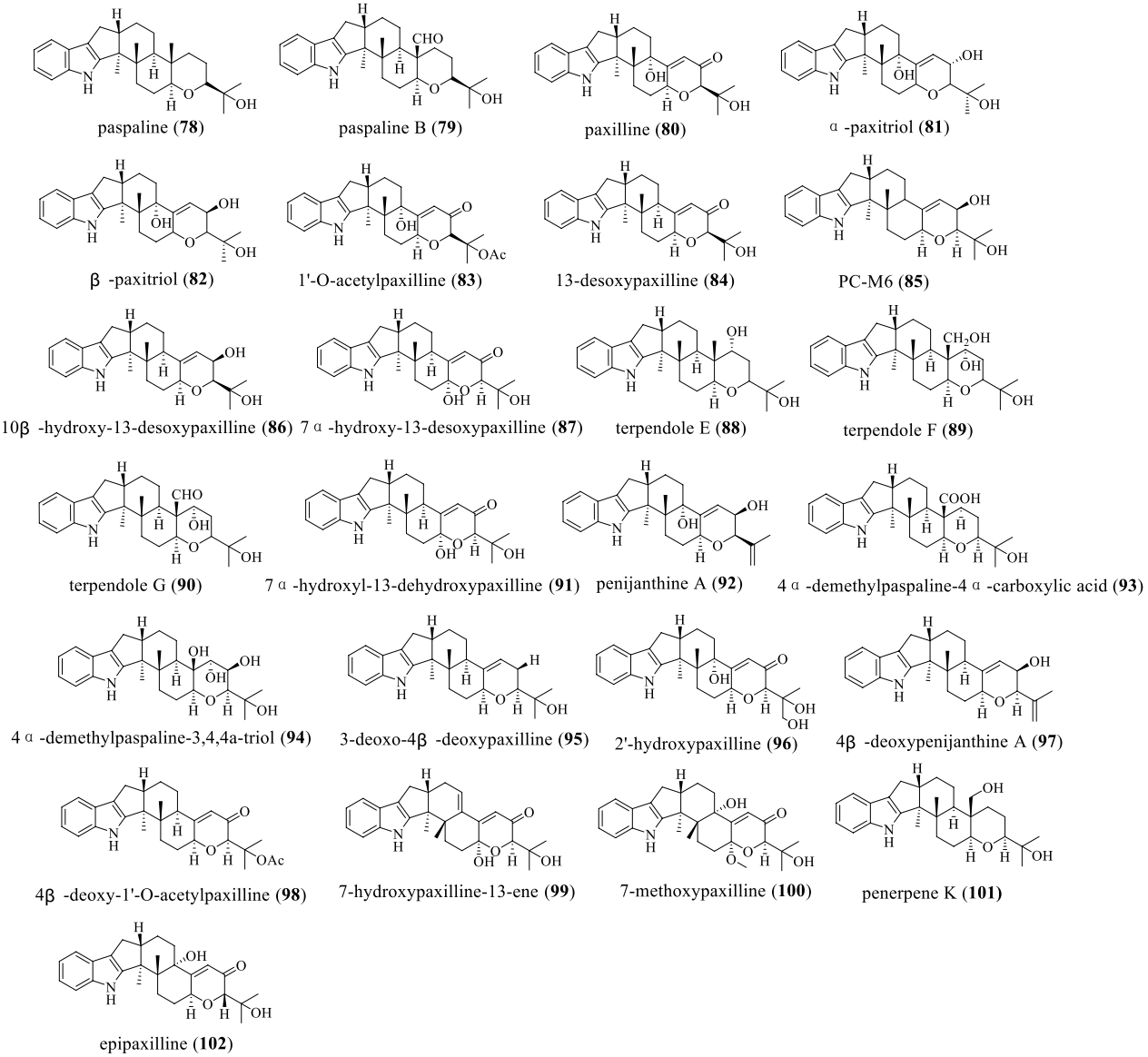



**Fig. 7** Chemical structures of paspaline-type compounds with only a paspaline skeleton

levels, the two compounds resulted in a 90% reduction in body weight gain in tests against the corn roundworm *H. zea*. However, at this concentration, **105** does not have any effect [69]. In 1995, Huang XH et al. isolated and characterized terpendole A (**107**), B (**108**), C (**109**), and D (**110**) from *Albophoma yamanashiensis* and found that they showed strong inhibition of ACAT activity [70]. In 1995, Tomoda et al. isolated and characterized terpendoles H–K (**111**–**114**) from the culture broth of *A. yamanashiensis* using different production media [62]. **113** and **114** have moderate inhibitory effects on ACAT activity with $IC_{50}$ values of 38.8 μm and 38.0 μm in rat liver microsomes, respectively, but **114** has a weaker activity [62–64]. In 1999, terpendole M (**115**) was isolated from perennial ryegrass (*Lolium perenne*) infected with the endophytic fungus *Neotyphodium lolii*. In standard mouse bioassays, this compound was less tremor than **109** [71]. In 2006, Junker et al. isolated and discovered the compound 14-(N,N-dimethylleucyloxy)-paspalinine (**116**) from *Aspergillus alliaceus* culture medium by optimizing the culture conditions [72]. In 2016, Gao et al. discovered the compound rhizovarins F (**117**) from Rhizomucor *Mucor irregularis* QEN-189 [49]. In 2019, Liang JH and colleagues isolated a new IDT drechmerin I (**118**) from the fermentation broth of *Drechmeria* sp., which has antibacterial activity against

**Table 7** Name, bioactivities and source of compounds with only paspaline skeleton

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **78** | Paspaline | Anti-cancer | *C. paspali* | [23] |
| **79** | Paspaline B | Tremor activity | *Penicillium* sp. | [55] |
| **80** | Paxilline | Tremor and bacteriostatic activity | *P. paxilli* | [57] |
| **81** | α-Paxitriol | Tremor activity | *P. paxilli* | [43] |
| **82** | β-Paxitriol | Tremor activity | *P. paxilli* | [43] |
| **83** | 1′-O-Acetylpaxilline | Tremor activity | *E. striata* | [29] |
| **84** | 13-Desoxypaxilline | Anti-cancer | *Emericella* spp. | [58] |
| **85** | PC-M6 | Antibacterial activity | *Penicillium* sp. | [59] |
| **86** | 10β-Hydroxy-13-desoxypaxilline | Cell activity | *P. paxilli* | [61] |
| **87** | 7α-Hydroxy-13-desoxypaxilline | Tremor activity | *P. paxilli* | [61] |
| **88** | Terpendole E | Mitotic kinesin | *Chaunopycnis alba* | [63] |
| **89** | Terpendole F | Weak activity | *A. yamanashiensis* | [62] |
| **90** | Terpendole G | Weak activity | *A. yamanashiensis* | [62] |
| **91** | 7α-Hydroxyl-13-dehydroxypaxilline | Antibacterial activity | *E. Shearii* | [65] |
| **92** | Penijanthine A | | *P. janthinellum* | [66] |
| **93** | 4α-Demethylpaspaline-4α-carboxylic acid | Cytotoxicity | *P. camemberti* | [7] |
| **94** | 4α-Demethylpaspaline-3,4,4α-triol | Cytotoxicity | *P. camemberti* | [7] |
| **95** | 3-Deoxo-4β-deoxypaxilline | Cytotoxicity | *camemberti* | [7] |
| **96** | 2′-Hydroxypaxilline | | *P. camemberti* | [7] |
| **97** | 4β-Deoxypenijanthine A | | *Penicillium* sp. | [67] |
| **98** | 4β-Deoxy-1′-O-acetylpaxilline | | *Penicillium* sp. | [67] |
| **99** | 7-Hydroxypaxilline-13-ene | Cytotoxicity | *Penicillium* sp. | [42] |
| **100** | 7-Methoxypaxilline | | *Penicillium* sp. | [42] |
| **101** | Penerpene K | Inhibitory activity against PTP1B and TCPTP | *Penicillium* sp. | [35] |
| **102** | Epipaxilline | Anti-cancer | *Penicillium* sp. | [26] |

*Bacillus subtilis* with a MIC value of 200 μg/mL [73]. In 2019, during chemical research on the endophyte *Penicillium* sp. ZO-R1-1 isolated from the root of the medicinal plant ginger, paspalinine-13-ene (**119**), was discovered, which shows cytotoxicity with $IC_{50}$ values in the range of 5.3–8.1 μM [42]. In 2020, the compound terpendole P (**120**) was isolated from the culture medium of the fungus *Volutella citrinella* BF-0440, which has 6 consecutive ring systems and an indole ring and can inhibit sterol O-acyltransferases 1 and 2 (SOAT1 and 2) [52]. In 2021, the compound ascandinine C (**121**) was isolated from the Antarctic sponge-derived fungus *Aspergillus candidus* HDN15-152. It is a rare IDT with a 6/5/5/6/6/6/6-fused ring system. The compound **121** has anti-influenza virus A (H1N1) activity with an $IC_{50}$ value of 26 μM [53]. In 2021, the IDT penerpene L (**122**) was isolated from a fermentation broth produced by adding L-tryptophan to the medium of the fungus *Penicillium sp.* KFD28. It has inhibitory activity against PTP1B and TCPTP, but has no antibacterial activity and cytotoxicity [35]. In the same year, the IDTs ascandinine B (**124**) and D (**125**) were isolated from the Antarctic sponge-derived fungus *Aspergillus candidus* HDN15-152. They represent a rare IDT with a 6/5/5/6/6/6/6-fused ring system. Among them, **125** is cytotoxic to HL-60 cells with an $IC_{50}$ value of 7.8 μM [53].

### 3.3 A-ring prenylation

Based on the paspaline skeleton, the modification of isopentenyl was added to the 20, 21 or (and) 22 positions of the **A** ring of its indole ring (Fig. 9 and Table 9). In 1964, Wilson BJ isolated the compounds α-aflatrem (**126**) and β-aflatrem (**127**) from *Aspergillus flavus*, which are fibrillating mycotoxins with acute neurotoxic effects [74, 75]. In 1977, Cole RJ et al. discovered the compound paspalitrem A (**128**) from *Claviceps paspali*, a toxin that can vibrate muscles [76, 77]. In 1992, compounds sulpinine A (**129**) and B (**130**) were isolated from *Aspergillus sulphureus*, both of which were active against *H. zea* but not against *C. hemipterus* [44]. Among them, **129** have the most potent activity. When this compound was added to the standard test diet at 100 ppm, a 96.0% reduction in body weight gain compared to the control was noted after one week, and a 10% mortality rate was also observed in this assay. **130** brought a similar weight gain reduction of 87.2%. Moreover, **129** was also cytotoxic to human lung cancer A549, breast cancer MCF7,

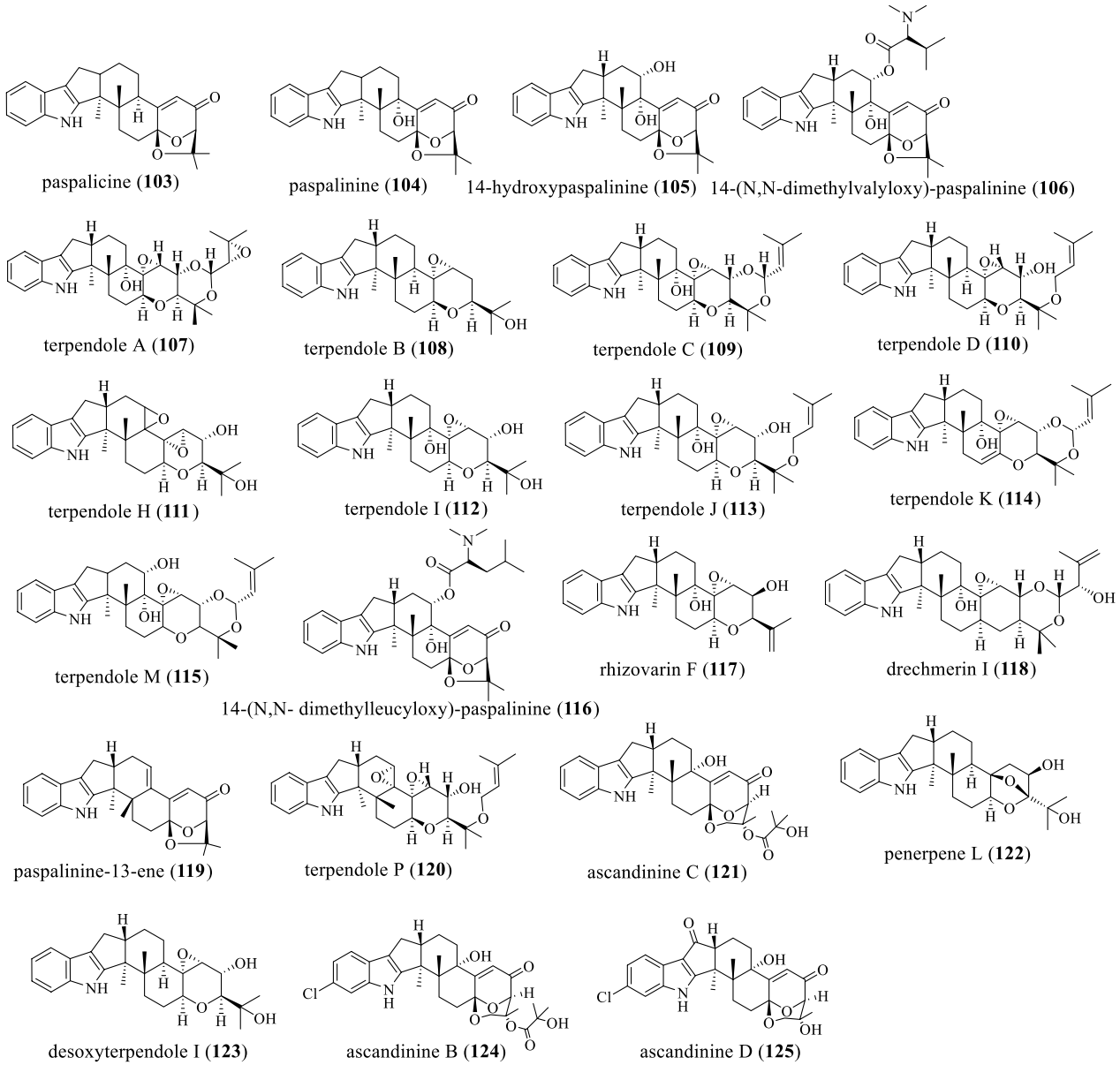



**Fig. 8** Chemical structures of paspaline-type compounds with F-ring modification

and colon adenocarcinoma HT-29 cells with $ED_{50}$ values of 25.7, 58.1, and 3.7 μg/ mL [44, 78]. In 1995, Tomoda H et al. isolated and characterized terpendole L (**131**) from the culture broth of *Albophoma yamanashiensis* by using different production media [62]. This compound has a moderate inhibitory effect on ACAT activity with an $IC_{50}$ value of 32.4 μM in rat liver microsomes [62–64]. In 1996, the first systematic study of the effect of paspalitrem C (**132**) on the spontaneous contractile activity of a variety of mammalian smooth muscles [79], increased the spontaneous contractility of the bladder and duodenum in guinea pigs and rats, and caused tracheal tension in guinea pigs. These effects are attributed to blocking high conductance, $Ca^{2+}$-activated $K^{+}$ channels [77, 79]. In 2007, shearinine K (**133**) and J (**134**) were isolated and characterized from the endophytic fungus *Penicillium* sp. [80]. In 2013, the IDT 21,22-diprenylpaxilline (**135**) was isolated from an acid fungal strain *Penicillium camemberti* OUCMDZ-1492, which exhibits significant protection against H1N1 virus-induced cytopathic in MDCK cells with an $IC_{50}$ value of 73.3 μM [7]. In 2014, when studying JanD and AmyD protein function, the compound 20,21-diprenylpaxilline (**136**) were discovered [13, 81, 82]. In 2019, the isoprene IDT tolypocladin A (**137**)

**Table 8** Name, bioactivities and source of compounds with F-ring modification

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **103** | Paspalicine | Block maxi-K channels | *C. paspali* | [23] |
| **104** | Paspalinine | Vibratory mycotoxins | *P. tularense* | [68] |
| **105** | 14-Hydroxypaspalinine | Insect resistance | *Aspergillus nomius* | [69] |
| **106** | 14-(N,N-dimethylvalyloxy)-Paspalinine | Insect resistance | *Aspergillus nomius* | [69] |
| **107** | Terpendole A | ACAT inhibitors | *A. yamanashiensis* | [70] |
| **108** | Terpendole B | ACAT inhibitors | *A. yamanashiensis* | [70] |
| **109** | Terpendole C | Tremor activity | *A. yamanashiensis* | [70] |
| **110** | Terpendole D | ACAT inhibitors | *A. yamanashiensis* | [70] |
| **111** | Terpendole H | Weak activity | *A. yamanashiensis* | [62] |
| **112** | Terpendole I | ACAT inhibitors | *A. yamanashiensis* | [62] |
| **113** | Terpendole J | ACAT inhibitors | *A. yamanashiensis* | [62] |
| **114** | Terpendole K | Tremor activity | *I. muelleri* | [62] |
| **115** | Terpendole M | ACAT inhibitors | *N. lolii* | [71] |
| **116** | 14-(N,N-dimethylleucyloxy)-Paspalinine | | *Aspergillus alliaceus* | [72] |
| **117** | Rhizovarin F | | *Mucor irregularis* | [49] |
| **118** | Drechmerin I | Antibacterial activity | *Drechmeria* sp. | [73] |
| **119** | Paspalinine-13-ene | Cytotoxicity | *Penicillium* sp. | [42] |
| **120** | Terpendole P | Suppress SOAT | *Volutella citrinella* | [52] |
| **121** | Ascandinine C | Cytotoxicity | *A. candidus* | [53] |
| **122** | Penerpene L | Inhibitory activity against PTP1B and TCPTP | *Penicillium* sp. | [35] |
| **123** | Desoxyterpendole I | | | [13] |
| **124** | Ascandinine B | | *A. candidus* | [53] |
| **125** | Ascandinine D | Cytotoxicity | *A. candidus* | [53] |

was isolated from the fungus *Tolypocladium* sp., which showed no inhibitory activity against three pathogenic fungi (*F. oxysporum*, *A. solani*, and *R. solani*). However, it showed significant inhibitory activity against seven pathogenic fungi (*A. fragariae, C. cassiicola, A. alternata, B. cinereal, C. personata, V. dahliae Kleb,* and *S. sclerotiorum*), with MIC values of 6.25–25 μg /mL. It is also active against *Bacillus cereus* and *Staphylococcus aureus*,with MIC values of 25 and 12.5 μg/mL, respectively [51]. In 2019, two new prenylated IDTs, namely tolypocladin K (**138**) and L (**139**), were isolated from the fungus *Tolypocladium* sp. XL115. The compound **138** exhibits moderate antifungal activity against *S. sclerotiorun, H. maydis, B. cinereal,* and *C. acutatum* with a MIC value of 50 μg/mL [64].

### 3.4 The isopentenyl group on the A ring is modified

The difference from the previous classification is that the isopentenyl group on the **A** ring is further modified by oxidation, halogenation, or epoxidation (Fig. 10 and Table 10). In 1977, Cole et al. discovered the compound paspalitrem B (**140**) from *Claviceps paspali* [76]. Cattle are affected by tremors (also known as "staggering") as they graze on toxic pastures; the compound identified at the highest concentration was the compound **140** (~ 150 mg/kg) in *Claviceps cynodontis*-infected *Cynodon dactylon* collected from pastures causing staggered syndrome in South African cattle herds [76, 77]. In 1990, PC-M5 (**141**) was isolated from *Penicillium crustosum*, which is toxic to PC12 cells [35, 59, 60]. In 2002, Tsuchiya et al. found the isolated and characterized compound NK12838 (**142**), which inhibits the activities of SOAT1 and SOAT2 with a SI value (log ($IC_{50}$ for SOAT1)/($IC_{50}$ for SOAT2)) of + 0.27, but has no cytotoxicity [83, 84]. In 2016, while studying the biosynthesis of shearinine, the compound protoshearinine (**143**) was characterized [85]. In 2018, the compound sespelline (**144**) was reported while studying the biosynthesis of sespendole [86]. In 2019, new isoprenindole diterpenes tolypocladins B–G (**145**–**150**), I (**151**), and J (**152**) were isolated from the fungus *Tolypocladium* sp., they showed no inhibitory activity against three pathogenic fungi (*F. oxysporum*, *A. solani* and *R. solani*). All of them are active against *A. fragariae* with MIC values of 6.25–50 μg/mL, and compound **145** has weak activity against *Staphylococcus aureus* [51]. In 2020, the compound terpendole O (**153**) was isolated from the culture medium of the fungus *Volutella citrinella* BF-0440, which has 7 consecutive ring systems and an indole ring. It can inhibit sterol SOAT1 and 2 [52]. In 2020, Ohshiro T and colleagues

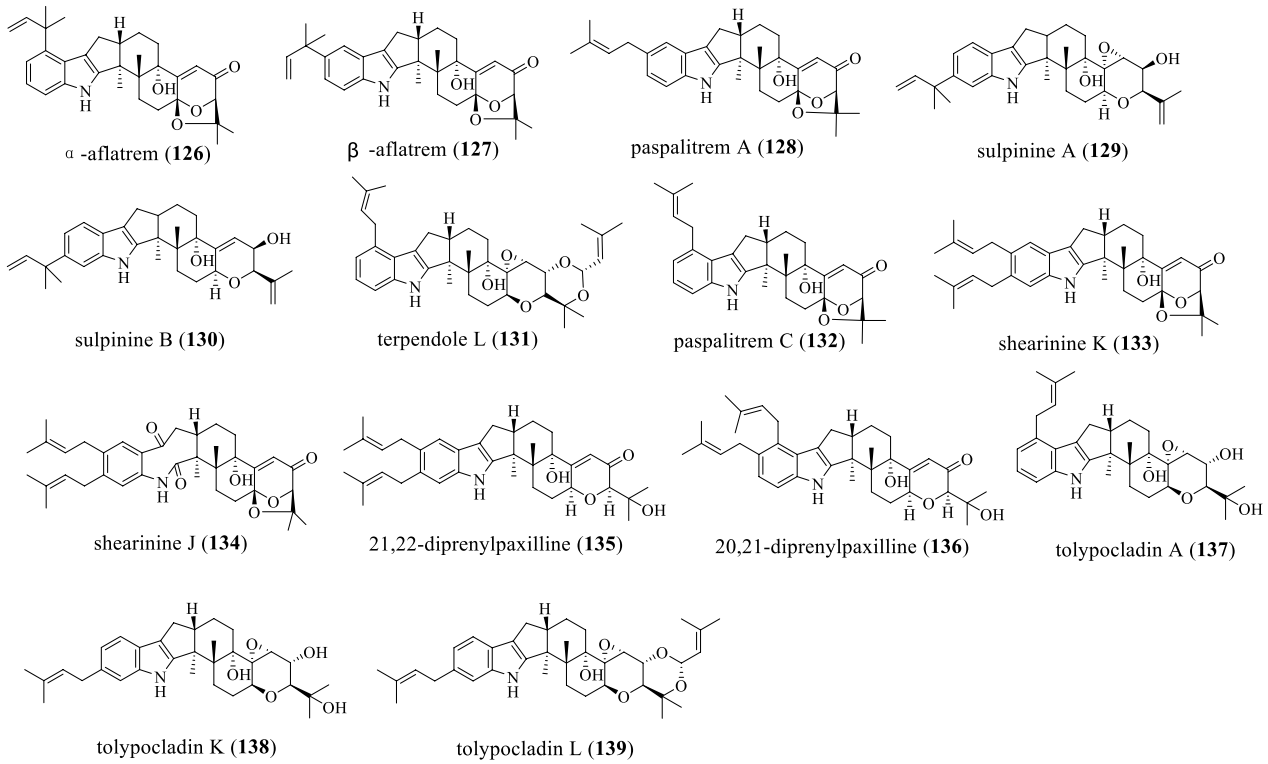



**Fig. 9** Chemical structures of paspaline-type compounds with A-ring prenylation

**Table 9** Name, bioactivities and source of compounds with A-ring prenylation

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **126** | α-Aflatrem | Neurotoxicity | *A. flavus* | [74] |
| **127** | β-Aflatrem | Neurotoxicity | *A. flavus* | [74] |
| **128** | Aaspalitrem A | Tremor muscle toxin | *C. paspali* | [76] |
| **129** | Sulpinine A | Anti-insect, cytotoxic | *A. sulphureus* | [44] |
| **130** | Sulpinine B | Anti-insect | *A. sulphureus* | [44] |
| **131** | Terpendole L | Antibacterial activity | *Tolypocladium* sp. | [64] |
| **132** | Paspalitrem C | Tremor muscle toxin | *Phomopsis* sp. | [79] |
| **133** | Shearinine K | | *P. janthinellum* | [80] |
| **134** | Shearinine J | | *Penicillium* sp. | [80] |
| **135** | 21,22-Diprenylpaxilline | Cytotoxic | *P. camemberti* | [7] |
| **136** | 20,21-Diprenylpaxilline | | | [81] |
| **137** | Tolypocladin A | Antibacterial activity, cytotoxic | *Tolypocladium* sp. | [51] |
| **138** | Tolypocladin K | Antifungal activity | *Tolypocladium* sp. | [64] |
| **139** | Tolypocladin L | | *Tolypocladium* sp. | [64] |

isolated new compounds, termed voluhemins A (**154**) and B (**155**), from the culture broth of the fungal strain *Volutella citrinella* BF 0440. They have a common IDT core and two additional isoprenyl moieties, and **155** are O-methylated **154**. **154** can inhibit the activities of SOAT1 and SOAT2 with a SI value of + 0.45, and **155** can selectively inhibit the SOAT2 isoenzyme. However, none of which is cytotoxic [83].

### 3.5 A-ring with 6/5 member ring

The 21 and 22 positions of the **A**-ring of the indole ring are modified with diprenyl groups, and then further

oxidatively cyclized into a 6/5-membered ring (Fig. 11 and Table 11). In 1984, Jesus et al. isolated and identified the tremor toxin janthitrems E–G (**156**–**158**) from the fungus *P. janthinellum* [87]. In 1992, Wilkins et al. isolated janthitrem B (**159**) [88]. In 1993, Penn and colleagues isolated and identified the compound janthitrem C (**160**) [89]. In 1995, compounds shearinines A (**161**) and B (**162**) were discovered from the fungus *Eupenicillium shearii*, both of which showed potent activity against *H. zea* and *Carpophilus hemipterus* [65]. **161** also induces apoptosis in human leukemia HL-60 cells, while **162** causes significant mortality in leaf disc assays against *Spodoptera frugiperda* [65, 90]. In 1995, Belofsky et al. discovered the compound shearinine C (**163**) from *Eupenicillium Shearii*, which can be formed from **160** through an autoxidative process, which has anti-insect activity [65]. In 2007, Smetanina OF and colleagues isolated shearinines D(**164**), E(**165**),and F(**166**) from marine-derived strains of the fungus *Penicillium janthinellum* [90]. **166** inhibits EGF-induced malignant transformation of JB6 $P^+$ Cl 41 cells in soft agar with INCC50 (inhibition of colony number 50) equal to 13 μM concentration. It may be a strongly effective cancer preventive agent in humans or animals. **164** and **165** induce apoptosis in human leukemia HL-60 cells at a concentration of 100 μM. Moreover, the apoptosis rates of apoptotic cells are 39% and 34%, respectively, compared with control cells [80, 90]. In 2007, shearinines D–G was isolated and characterized from the endophytic fungus *Penicillium* sp., in which shearinine G (**167**) had inhibitory effects on BK channels [80]. Shearinines H (**168**) and I (**169**) were isolated and characterized from the endophytic fungus *Penicillium* sp. in 2007 [80]. In 2010, the compound epoxy-janthitrems I–IV (**170**–**173**) was isolated and identified from the endophyte *Epichloë endophytes*, and the compound epoxy-Janthitrems produced by the endophyte had strong inhibitory activity against insect larvae. However, when ryegrass plants are grown at a constant low temperatures for a long time, the concentration of the compounds in the plants is significantly reduced, and the insect resistance is less effective [91, 92]. In 2014, the compound pyrapaxilline (**174**) was isolated from *Eupenicillium shearii.* Lipopolysaccharide (LPS) increases NO production by approximately 2.5-fold over basal levels. When the mouse macrophage cell line RAW264.7 was pretreated with this compound for 2 h before LPS stimulation, it inhibited NO production by 40% at 10–30 μg/ml with no toxicity [93]. In 2018, new compounds 11,12-epoxyjanthitrem B and 11,12-epoxyjanthitrem C were isolated from the fungus *Penicillium janthinellum*,

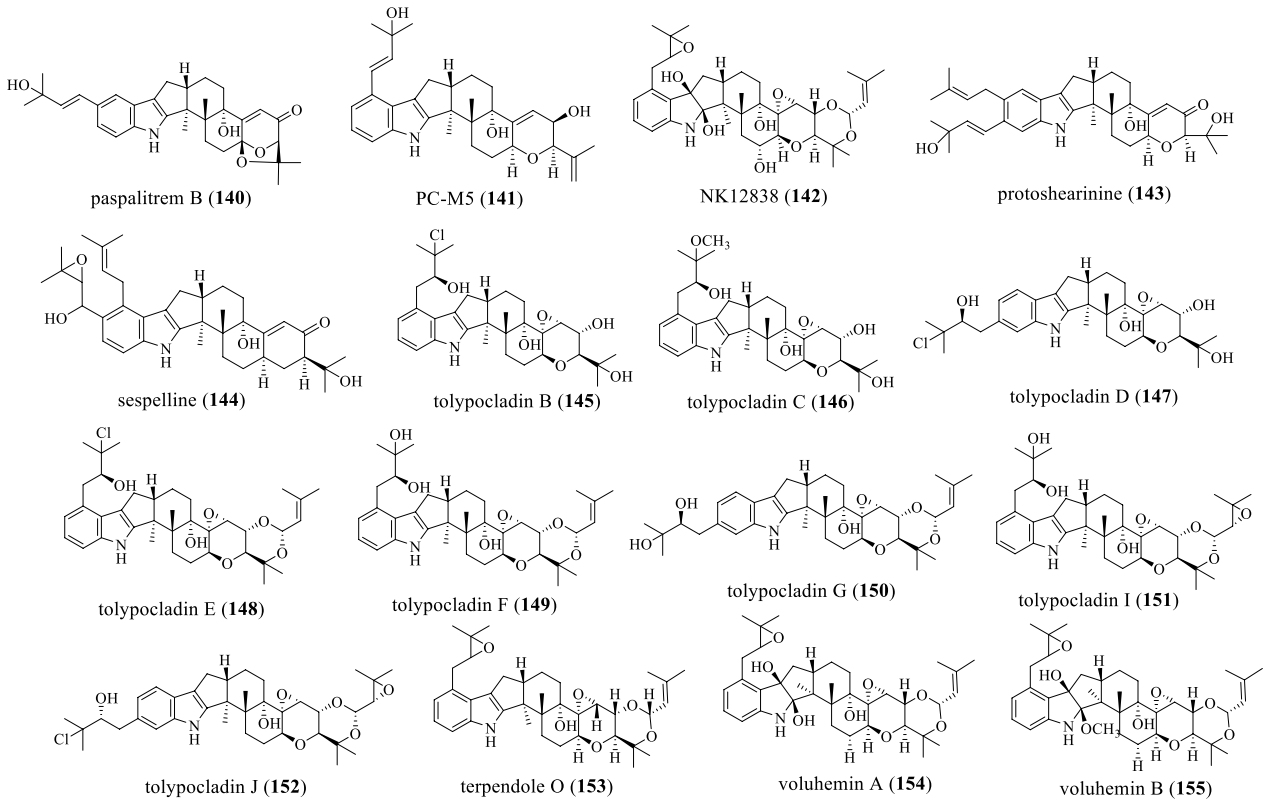



**Fig. 10** Chemical structures of paspaline-type compounds in which the isopentenyl group on the A-ring is modified

**Table 10** Name, bioactivities and source of compounds with the isopentenyl group on the A-ring is modified

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **140** | Paspalitrem B | Tremor muscle toxin | *C. paspali* | [76] |
| **141** | PC-M5 | Cytotoxicity | *P. crustosum* | [59] |
| **142** | NK12838 | Inhibits SOAT1 and SOAT2 activity | *V. citrinella* | [84] |
| **143** | Protoshearinine | | | [85] |
| **144** | Sespelline | | | [86] |
| **145** | Tolypocladin B | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **146** | Tolypocladin C | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **147** | Tolypocladin D | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **148** | Tolypocladin E | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **149** | Tolypocladin F | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **150** | Tolypocladin G | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **151** | Tolypocladin I | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **152** | Tolypocladin J | Antibacterial activity | *Tolypocladium* sp. | [51] |
| **153** | Terpendole O | Suppress SOAT | *Volutella citrinella* | [52] |
| **154** | Voluhemin A | Inhibits SOAT1 and SOAT2 activity | *V. citrinella* | [83] |
| **155** | Voluhemin B | Inhibit SOAT2 activity | *V. citrinella* | [83] |

and named janthitrem A (**175**) and janthitrem D (**176**), respectively. Injecting mice with **175** at a concentration of 4 mg/kg can achieve high-intensity tremor effects in 15 min [94]. In 2019, Ariantari NP and colleagues isolated compounds shearinine P (**177**), 7-methoxyshearinine P (**178**), and shearinine Q (**179**) from strain *Penicillium sp.* ZO-R1-1. Among them, the $IC_{50}$ value of **179** on L5178Y or A2780 cells is 10 μM [42]. In 2019, during chemical research on the endophyte *Penicillium sp.* ZO-R1-1 isolated from the medicinal plant ginger root, the compounds 7-methoxypyrapaxilline (**180**) and pyrapaxilline-6-ene (**181**) were discovered. Among them, the compound **181** showed cytotoxicity with $IC_{50}$ values in the range of 5.3–8.1 μM; and also showed significant cytotoxic activity against the A2780 human ovarian cancer cell line, with $IC_{50}$ values of 5.3–8.7 μM [42].

### 3.6 A-ring with 5/6 member ring

The difference from the previous type is that this type is further oxidatively cyclized into a 5/6-membered ring based on the diprenyl modification at the 20 and 21 positions of the **A** ring of the indole ring (Fig. 12 and Table 12). In 1981, two strong neurotoxins, lolitrems A (**182**) and B (**183**), were isolated from herbs that developed a livestock disease known as "ryegrass staggered disease." They can poison livestock with tremors that do not directly impair spatial learning and memory, but reduce voluntary movements in poisoned animals; later, perennial ryegrass toxicosis (PRGT) was prevented by limiting the concentration of **183** [95]. In 1992, lolitriol (**184**) was found in extracts of endophyte-infected ryegrass leaves and cultures of *A. lolii* [43]. Moreover, **183** is quickly degraded to compound **184**, which does not cause tremors even at 20 mg/kg, so its activity is at least 20-fold lower than **183** [96]. In 1994, Christopher et al. obtained the abundant secondary compound lolitrem E (**185**) when **183** was purified from ryegrass staggers (RGS), which has intense BK channel activity but no tremor effect in animals [97, 98]. In 1996, Sarah et al. isolated lolitrem F (**186**), a stereoisomer of the vibratory mycotoxin **183**, from ryegrass infected with *Acremonium Lolii*. The compound **186** was found to have similar potency and duration of action as **183** in standard mouse bioassays, but was slightly less active than **183** [99]. In 1997, the compound lolitrem H (**187**) was discovered [71]. In 1997, Sarah et al. isolated lolilline (**188**) from an extract of ryegrass seeds infected with the endophytic fungus *Acremonium lolii*, which does not have tremor effects [100]. In 1998, lolitrem N (**189**), lolicine A (**190**), and B (**191**) were identified in an extract of perennial ryegrass (*Lolium perenne*) seeds infected with the endophytic fungus *Neotyphodium lolii*, and they are lolitrem-like compounds [101].

### 3.7 A-ring 4/5 or 6 membered ring

The difference between this type and the last type is that the oxidative cyclization is modified into a 4/5 or 4/6-membered ring, and even further forms an oxygen-containing 8-membered ring with the 17th position of the **C** ring (Fig. 13 and Table 13). In 1983, Amelia et al. isolated 6 IDTs penitrems A–F (**192**–**197**) from *Penicillium crustosum*, wherein the compounds **192**, **194**, and **197** showed the anti-cancer effect on human A-549 and HL-60 cancer cell lines

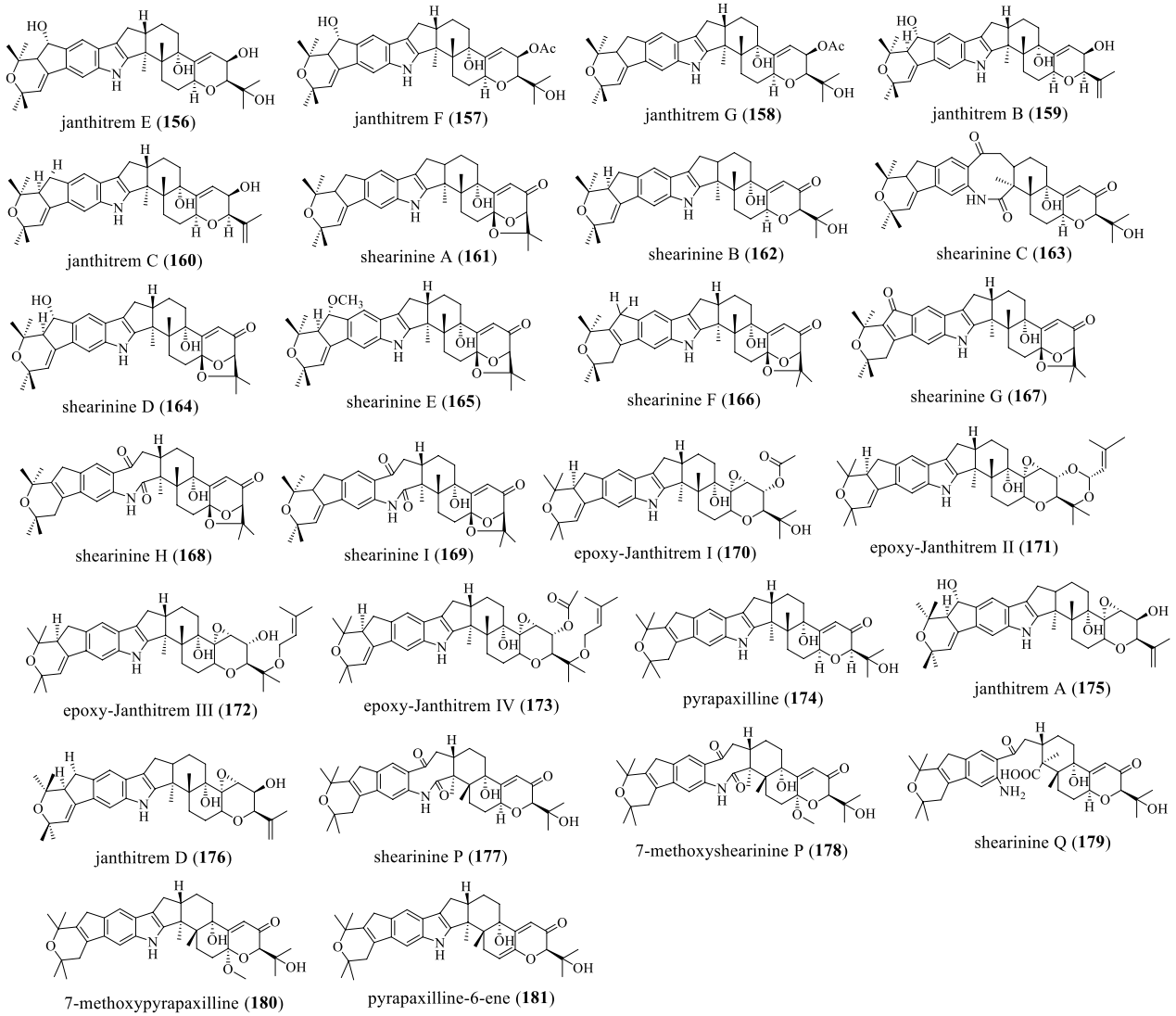



**Fig. 11** Chemical structures of paspaline-type compounds with A-ring 6/5 member ring

[49, 102]. It was also found that all chlorinated compounds (**192**, **194**, and **197**) exhibited more vigorous activity than their chlorine-free analogs, **193**, **195**, and **196** [24, 49]. In 1992, the compound secopenitrem B (**198**) was isolated from *Aspergillus sulphureus*, which was active against *H. zea* but inactive against *C. hemipterus*. It reduced weight gain by 87.0%, while **198** also caused 32.0% larval mortality [44]. In 1993, Yamaguchi et al. isolated PC-M4 (**199**) from *P. crustosum*, which could be biosynthesized by PC-M6, and then added isoprenyl to give PC-M5, which had no cancer cell activity [59]. In 2011, the compound secopenitrem D (**200**) was isolated and characterized from *P. crustosum*, which caused poisoning in animals [103]. In 2016, Gao et al. discovered the compounds rhizovarins A–C (**201**–**203**) and E (**204**) from Rhizomucor *Mucor irregularis* QEN-189, which represent the most complex members of the IDT derivatives. Among them, **201** and **202** showed activity against human A-549 and HL-60 cancer cell lines, and compound **204** showed activity against the A-549 cancer cell line, but not the Hela cell line [49].

## 4 Conclusion

This paper reviews the chemical structures of IDTs and their derivatives discovered in the past 50 years. Based on previous classifications, we divided 77 non-paspaline compounds into 6 categories according to their structural characteristics, and 127 paspaline-type compounds are divided into 7 categories according to

**Table 11** Name, bioactivities and source of compounds with A-ring 6/5 member ring

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **156** | Janthitrem E | Tremor toxin | *P. janthinellum* | [87] |
| **157** | Janthitrem F | Tremor toxin | *P. janthinellum* | [87] |
| **158** | Janthitrem G | Tremor toxin | *P. janthinellum* | [87] |
| **159** | Janthitrem B | Tremor, anti-insect activity | *P. janthinellum* | [88] |
| **160** | Janthitrem C | | *P. janthinellum* | [89] |
| **161** | Shearinine A | Anti-insect, cancer cell activity | *E. shearii* | [65] |
| **162** | Shearinine B | Anti-insect activity | *E. shearii* | [65] |
| **163** | Shearinine C | anti-insect activity | *E. shearii* | [65] |
| **164** | Shearinine D | cancer cell activity | *P. janthinellum* | [80] |
| **165** | Shearinine E | Anti-cancer | *P. janthinellum* | [80] |
| **166** | Shearinine F | | *Penicillium* sp. | [80] |
| **167** | Shearinine G | BK channel inhibition | *Penicillium* sp. | [80] |
| **168** | Shearinine H | | *Penicillium* sp. | [80] |
| **169** | Shearinine I | | *Penicillium* sp. | [80] |
| **170** | Epoxy-Janthitrem I | Pesticide | *E. endophytes* | [91] |
| **171** | Epoxy-Janthitrem II | Pesticide | *E. endophytes* | [91] |
| **172** | Epoxy-Janthitrem III | Pesticide | *E. endophytes* | [91] |
| **173** | Epoxy-Janthitrem IV | Pesticide | *E. endophytes* | [91] |
| **174** | Pyrapaxilline | Inhibit the production of NO | *E. shearii* | [93] |
| **175** | Janthitrem A | Tremor, anti-insect activity | *P. janthinellum* | [94] |
| **176** | Janthitrem D | | *P. janthinellum* | [94] |
| **177** | Shearinine P | | *Penicillium* sp. | [42] |
| **178** | 7-Methoxyshearinine P | | *Penicillium* sp. | [42] |
| **179** | Shearinine Q | | *Penicillium* sp. | [42] |
| **180** | 7-Methoxypyrapaxilline | | *Penicillium* sp. | [42] |
| **181** | Pyrapaxilline-6-ene | Cytotoxicity | *Penicillium* sp. | [42] |

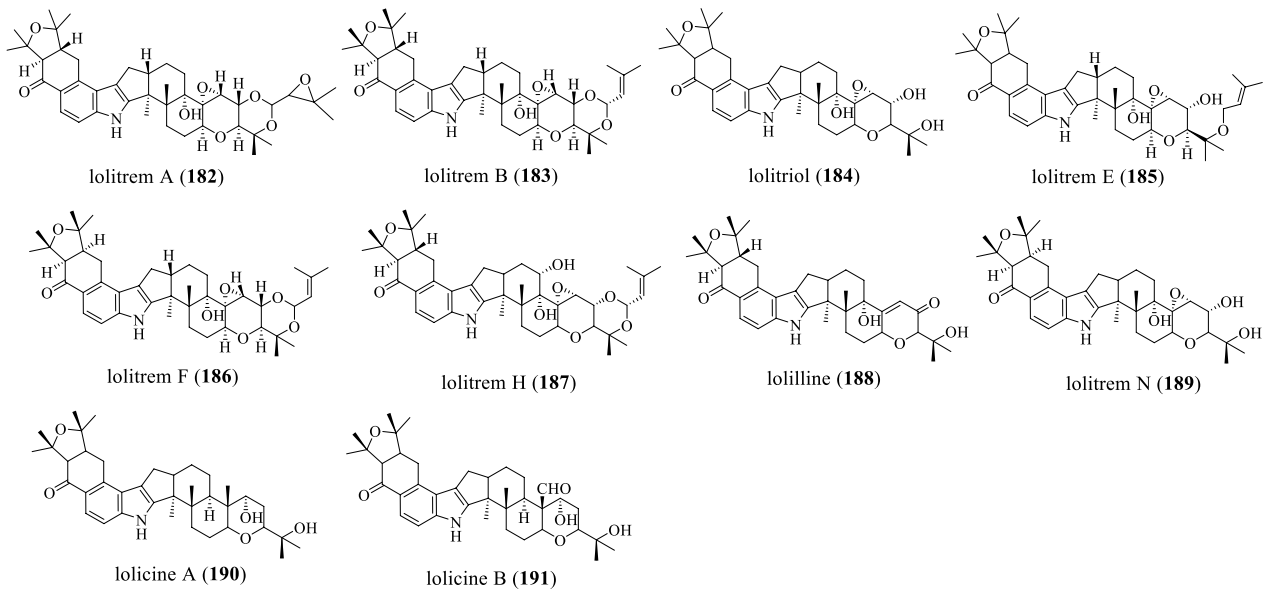



**Fig. 12** Chemical structures of paspaline-type compounds with A-ring 5/6 member ring

**Table 12** Name, bioactivities and source of compounds with A-ring 5/6 member ring

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **182** | Lolitrem A | Neurotoxin | *E. festucae* | [95] |
| **183** | Lolitrem B | Neurotoxin | *E. festucae* | [95] |
| **184** | Lolitriol | Neurotoxin | *Endophyte-infected ryegrass* | [43] |
| **185** | Lolitrem E | BK channel activity | *Endophyte-infected perennial ryegrass* | [97] |
| **186** | Lolitrem F | Neurotoxin | *L. perenne* | [99] |
| **187** | Lolitrem H | | *A. lolii* | [71] |
| **188** | Lolilline | | *A. lolii* | [100] |
| **189** | Lolitrem N | | *Endophyte-infected ryegrass* | [101] |
| **190** | Lolicine A | | *L. perenne* | [101] |
| **191** | Lolicine B | | *L. perenne* | [101] |

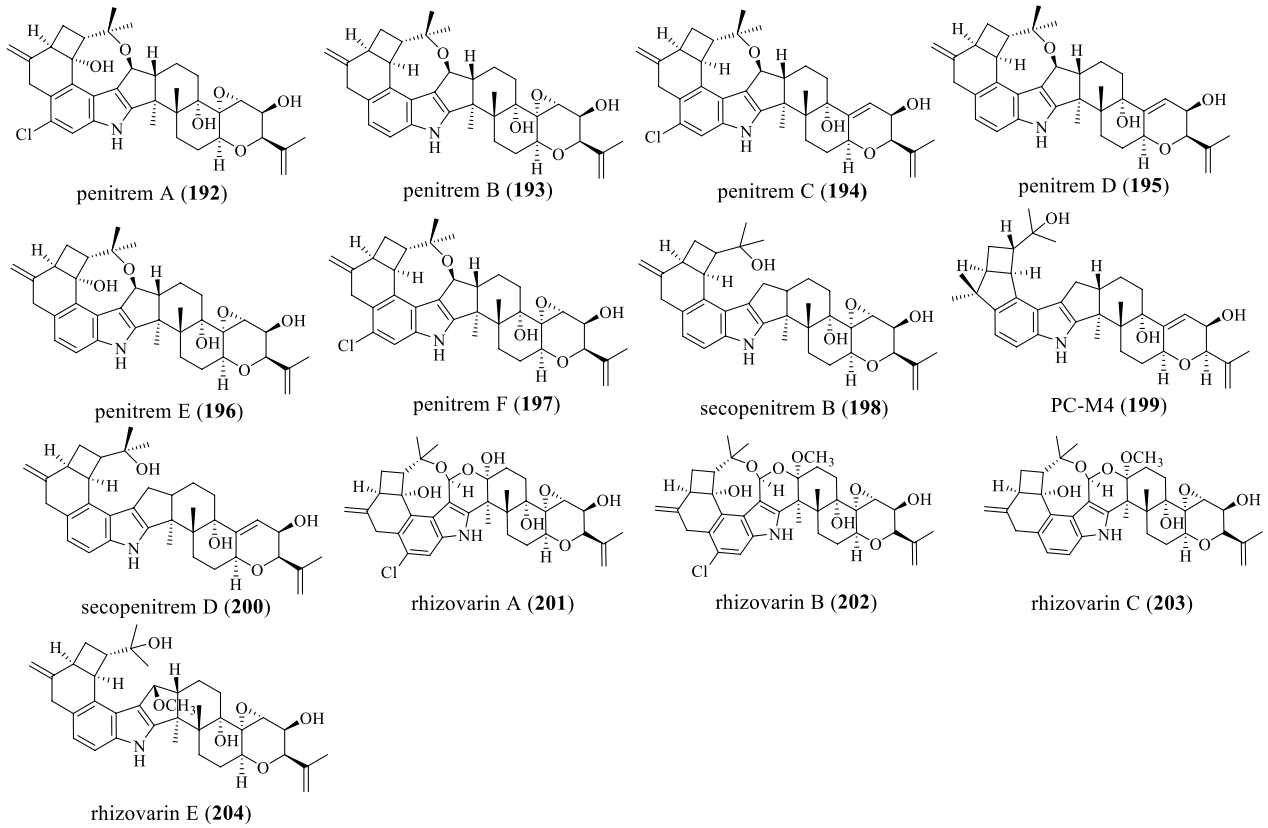



**Fig. 13** Chemical structures of paspaline-type compounds with A-ring 4/5 or 6 membered ring

oxidative modification. This provides convenient data for the future discovery of new compounds with similar structures or different oxidative modifications. At the same time, we also summarize the biophysiological activities of these compounds and their strong applications in pharmaceutical and agricultural markets. This also shows more compounds and provides more potent options for the development summary of future market applications.

**Table 13** Name, bioactivities and source of compounds with A-ring 4/5 or 6 membered ring

| Number | Compound name | Biological activity | Species origin | References |
|---|---|---|---|---|
| **192** | Penitrem A | Cancer cell activity | *P. crustosum* | [49] |
| **193** | Penitrem B | Anti-proliferative, anti-migration | *P. crustosum* | [49] |
| **194** | Penitrem C | Cancer cell activity | *P. crustosum* | [49] |
| **194** | Penitrem D | Anti-proliferative, anti-migration | *P. crustosum* | [49] |
| **196** | Penitrem E | Anti-proliferative, anti-migration | *P. crustosum* | [49] |
| **197** | Penitrem F | Cancer cell activity | *P. crustosum* | [49] |
| **198** | Secopenitrem B | Insect resistance | *A.sulphureus* | [44] |
| **199** | PC-M4 | | *P. crustosum* | [59] |
| **200** | Secopenitrem D | Poisons mammals | *P. crustosum* | [103] |
| **201** | Rhizovarin A | Cytotoxicity | *Mucor irregularis* | [49] |
| **202** | Rhizovarin B | Cytotoxicity | *Mucor irregularis* | [49] |
| **203** | Rhizovarin C | | *Mucor irregularis* | [49] |
| **204** | Rhizovarin E | Cytotoxicity | *Mucor irregularis* | [49] |

**Acknowledgements**
This work was funded by the National Natural Science Foundation of China (Project No. 22077102 and 21877089), and the Shaanxi Key Laboratory of Natural Product & Chemical Biology Open Foundation (Project No. SXNPCB 2021001).

**Author contributions**
All authors read and approved the final manuscript.

## Declarations

**Competing interests**
The author declares that there are no conflicts of interest associated with this work.

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Received: 14 October 2022 Accepted: 8 December 2022
Published: 3 January 2023

**References**

1. Saikia S, Nicholson MJ, Young C, Parker EJ, Scott B. The genetic basis for indole-diterpene chemical diversity in filamentous fungi. Mycol Res. 2008;112:184–99.
2. Andersen B, Frisvad JC. Natural occurrence of fungi and fungal metabolites in moldy tomatoes. J Agric Food Chem. 2004;52:7507–13.
3. Evans TJ, Gupta RC. Tremorgenic mycotoxins. In: Gupta RC, editor. Veterinary toxicology. Academic; 2018. p. 1033–41.
4. Roll DM, Barbieri LR, Bigelis R, McDonald LA, Arias DA, Li PC, et al. The lecanindoles, nonsteroidal progestins from the terrestrial fungus *Verticillium lecanii* 6144. J Nat Prod. 2009;72:1944–8.
5. Reddy P, Guthridge K, Vassiliadis S, Hemsworth J, Hettiarachchige I, Spangenberg G, et al. Tremorgenic mycotoxins: structure diversity and biological activity. Toxins (Basel). 2019;11:302.
6. Garcia ML, Goetz MA, Kaczorowski GJ, Mcmanus OB, Monaghan RL, Strohl WR, et al. U.S. Patent WO-03105724-A2, 13 Jun 2003.
7. Fan Y, Wang Y, Liu P, Fu P, Zhu T, Wang W, et al. Indole-diterpenoids with anti-H1N1 activity from the aciduric fungus *Penicillium camemberti* OUCMDZ-1492. J Nat Prod. 2013;76:1328–36.
8. Gloer JB, TePaske MR, Sima JS, Wicklow DT, Dowd PF. Antiinsectan aflavinine derivatives from the sclerotia of *Aspergillus flavus*. J Org Chem. 1988;53:5457–60.
9. Jesus AE, Gorst-Allman CP, Steyn PS, Heerden FR, Vleggaar R, Wessels PL, et al. Tremorgenic mycotoxins from *Penicillium crustosum*. Biosynthesis of penitrem A. J Chem Soc, Perkin Trans. 1983;1(1):1863–8.
10. Tagami K, Liu C, Minami A, Noike M, Isaka T, Fueki S, et al. Reconstitution of biosynthetic machinery for indole-diterpene paxilline in *Aspergillus oryzae*. J Am Chem Soc. 2013;135:1260–3.
11. Kozák L, Szilágyi Z, Tóth L, Pócsi I, Molnár I. Tremorgenic and neurotoxic paspaline-derived indole-diterpenes: biosynthetic diversity, threats and applications. Appl Microbiol Biot. 2019;103:1599–616.
12. Schatz DJ, Kuenstner EJ, George DT, Pronin SV. Synthesis of rearranged indole diterpenes of the paxilline type. Nat Prod Rep. 2022;39:946–68.
13. Liu CW, Minami A, Ozaki T, Oikawa H. Biosynthesis of indole diterpenes. Comprehensive natural products III: chemistry and biology. Elsevier 2022:446–66.
14. Minami A, Liu C, Oikawa H. Total biosynthesis of fungal indole diterpenes using cell factories. HETEROCYCLES. 2016;92:397–421.
15. Ozaki T, Minami A, Oikawa H. Biosynthesis of indole diterpenes: a reconstitution approach in a heterologous host. Nat Prod Rep. 2022. https://doi.org/10.1002/chin.201617243.
16. Ondeyka JG, Helms GL, Hensens OD, Singh SB, Etal EA. Nodulisporic acid A, a novel and potent insecticide from a *Nodulisporium* sp. isolation, structure determination, and chemical transformations. J Am Chem Soc. 1997;119:8809–16.
17. Meinke PT, Smith MM, Shoop WL. Nodulisporic acid: its chemistry and biology. Curr Top Med Chem. 2002;2:655–74.
18. Singh SB, Ondeyka JG, Jayasuriya H, Zink DL, Ha SN, Dahl-Roshak A, et al. Nodulisporic acids D-F: structure, biological activities, and biogenetic relationships. J Nat Prod. 2004;67:1496–506.
19. Hensens OD, Ondeyka JG, Dombrowski AW, Ostlind DA, Zink DL. Isolation and structure of nodulisporic acid A1 and A2, novel insecticides from a *Nodulisporium* sp. Tetrahedron Lett. 1999;40:5455–8.
20. Ondeyka JG, Dahl-Roshak AM, Tkacz JS, Zink DL, Zakson-Aiken M, Shoop WL, et al. Nodulisporic acid B, B1, and B2: a series of 1′-deoxynodulisporic acids from *Nodulisporium* sp. Bioorg Med Chem Lett. 2002;12:2941–4.
21. Ondeyka JG, Byrne K, Vesey D, Zink DL, Shoop WL, Goetz MA, et al. Nodulisporic acids C, C1, and C2: a series of D-ring-opened nodulisporic acids from the fungus *Nodulisporium* sp. J Nat Prod. 2003;66:121–4.

22. Zhang YH, Li L, Li YQ, Luo JH, Li W, Li LF, et al. Oxalierpenes A and B, unusual indole-diterpenoid derivatives with antiviral activity from a marine-derived strain of the fungus *Penicillium oxalicum*. J Nat Prod. 2022;85:1880–5.
23. Fehr T, Acklin W. Die isolierung zweier neuartiger indol-derivate aus dem mycel von *Claviceps paspali* STEVENSet HALL. Helv Chim Acta. 1966;49:1907–10.
24. Sallam AA, Ayoub NM, Foudah AI, Gissendanner CR, Meyer SA, El-Sayed KA. Indole diterpene alkaloids as novel inhibitors of the Wnt/β-catenin pathway in breast cancer cells. Eur J Med Chem. 2013;70:594–606.
25. Qiao MF, Ji NY, Liu XH, Li K, Zhu QM, Xue QZ. Indoloditerpenes from an algicolous isolate of *Aspergillus oryzae*. Bioorg Med Chem Lett. 2010;20:5677–80.
26. Chen MY, Xie QY, Kong FD, Ma QY, Zhou LM, Yuan JZ, et al. Two new indole-diterpenoids from the marine-derived fungus *Penicillium* sp. KFD28. J Asian Nat Prod Res. 2021;23:1030–6.
27. Chaiyosang B, Kanokmedhakul K, Yodsing N, Boonlue S, Yang JX, Wang YA, et al. Three new indole diterpenoids from *Aspergillus aculeatus* KKU-CT2. Nat Prod Res. 2022;36:4973–81.
28. Nozawa K, Nakajima S, Kawai K, Udagawa S. Studies on fungal products. Part 17. Isolation and structures of novel indoloditerpenes, emindoles DA and DB, from Emericella desertorum: X-ray molecular structure of emindole DA acetate. J Chem Soc. 1988;7:1689–94.
29. Nozawa K, Horie Y, Udagawa S, Kawai K, Yamazaki M. Isolation of a new tremorgenic indoloditerpene, 1′-O-acetylpaxilline, from *Emericella striata* and distribution of paxilline in *Emericella* spp. Chem Pharm Bull (Tokyo). 1989;37:1387–9.
30. Gloer JB, Rinderknecht BL, Wicklow DT, Dowd PF. Nominine: a new insecticidal indole diterpene from the sclerotia of *Aspergillus nomius*. J Org Chem. 1989;54:2530–2.
31. Laakso JA, Gloer JB, Wicklow DT, Dowd PF. Radarins A-D: new antiinsectan and cytotoxic indole diterpenoids from the sclerotia of *Aspergillus sulphureus*. J Org Chem. 1992;57:138–41.
32. Kimura Y, Nishibe M, Nakajima H, Hamasaki T, Shigemitsu N, Sugawara F, et al. Emeniveol: a new pollen growth inhibitor from the fungus, *Emericella nivea*. Tetrahedron Lett. 1992;33:6987–90.
33. Hosoe T, Itabashi T, Kobayashi N, Udagawa S, Kawai K. Three new types of indoloditerpenes, emindole PA—PC, from *Emericella purpurea*. Revision of the structure of emindole PA. Chem Pharm Bull (Tokyo). 2006;54:185–7.
34. Liu L, Xu W, Li S, Chen MY, Cheng YJ, Yuan WJ, et al. Penicindopene A, a new indole diterpene from the deep-sea fungus *Penicillium* sp. YPCMAC1. Nat Prod Res. 2019;33:2988–94.
35. Dai LT, Yang L, Kong FD, Ma QY, Xie QY, Dai HF, et al. Cytotoxic indole-diterpenoids from the marine-derived fungus *Penicillium* sp. KFD28. Mar Drugs. 2021;19:613.
36. Tepaske MR, Gloer JB, Wicklow DT, Dowd PF. Three new aflavinines from the sclerotia of *Aspergillus tubingensis*. Tetrahedron. 1989;45:4961–8.
37. Han X, Bao XF, Wang CX, Xie J, Song XJ, Dai P, et al. Cladosporine A, a new indole diterpenoid alkaloid with antimicrobial activities from *Cladosporium* sp. Nat Prod Res. 2021;35:1115–21.
38. TePaske MR, Gloer JB, Wicklow DT, Dowd PF. Tubingensin A: an antiviral carbazole alkaloid from the sclerotia of *Aspergillus tubingensis*. J Org Chem. 1989;54:4743–6.
39. Tepaske MR, Gloer JB, Wicklow DT, Dowd PF. The structure of tubingensin B: a cytotoxic carbazole alkaloid from the sclerotia of *Aspergillus tubingensis*. Tetrahedron Lett. 1989;30:5965–8.
40. Tepaske MR, Gloer JB, Wicklow DT, Dowd PF. Aflavazole: a new antiinsectan carbazole metabolite from the sclerotia of *Aspergillus flavus*. J Org Chem. 1990;55:5299–301.
41. Li H, Chen Q, Lu Z, Li A. Total syntheses of aflavazole and 14-hydroxyaflavinine. J Am Chem Soc. 2016;138:15555–8.
42. Ariantari NP, Ancheeva E, Wang C, Mándi A, Knedel TO, Kurtán T. Indole diterpenoids from an endophytic *Penicillium* sp. J Nat Prod. 2019;82:1412–23.
43. Miles CO, Wilkins AL, Gallagher RT, Hawkes AD, Munday SC, Towers NR. Synthesis and tremorgenicity of paxitriols and lolitriol: possible biosynthetic precursors of lolitrem B. J Agric Food Chem. 1992;40:234–8.
44. Laakso JA, Gloer JB, Wicklow DT, Dowd PF. Sulpinines A-C and secopenitrem B: new antiinsectan metabolites from the sclerotia of *Aspergillus sulphureus*. J Org Chem. 1992;57:2066–71.
45. Staub GM, Gloer J, Wicklow DT, Dowd PF. Aspernomine: a cytotoxic antiinsectan metabolite with a novel ring system from the sclerotia of *Aspergillus nomius*. J Am Chem Soc. 1992;114:1015–7.
46. Ooike M, Nozawa K, Udagawa S, Kawai K. Structures of a new type of indoloditerpene, petromindole, and a new asterriquinone derivative, PM-53, from the ascostromata of *Petromyces muricatus*. Chem Pharm Bull (Tokyo). 1997;45:1694–6.
47. Chen L, Gloer JB, Wicklow DT, Dowd PF. Thiersinines A and B: novel antiinsectan indole diterpenoids from a new fungicolous *Penicillium* species (NRRL 28147). Org Lett. 2002;4:3095–8.
48. Ogata M, Ueda JY, Hoshi M, Hashimoto J, Nakashima T, Anzai K, et al. A novel indole-diterpenoid, JBIR-03 with anti-MRSA activity from *Dichotomomyces cejpii* var. cejpii NBRC 103559. J Antibiot (Tokyo). 2007;60:645–8.
49. Gao SS, Li XM, Williams K, Proksch P, Ji NY, Wang BG. Rhizovarins A-F, indole-diterpenes from the mangrove-derived endophytic fungus *Mucor irregularis* QEN-189. J Nat Prod. 2016;79:2066–74.
50. Zhao JC, Luan ZL, Liang JH, Cheng ZB, Sun CP, Wang YL, et al. Drechmerin H, a novel 1(2), 2(18)-diseco indole diterpenoid from the fungus *Drechmeria* sp. as a natural agonist of human pregnane X receptor. Bioorg Chem. 2018;79:250–6.
51. Xu LL, Hai P, Zhang SB, Xiao JF, Gao Y, Ma BJ, et al. Prenylated indole diterpene alkaloids from a mine-soil-derived *Tolypocladium* sp. J Nat Prod. 2019;82:221–31.
52. Nur EAA, Kobayashi K, Amagai A, Ohshiro T, Tomoda H. New terpendole congeners, inhibitors of sterol O-acyltransferase, produced by *Volutella citrinella* BF-0440. Molecules. 2020;25:3079.
53. Zhou G, Sun C, Hou X, Che Q, Zhang G, Gu Q, et al. Ascandinines A-D, indole diterpenoids, from the sponge-derived fungus *Aspergillus candidus* HDN15-152. J Org Chem. 2021;86:2431–6.
54. Springer JP, Clardy J. Paspaline and paspalicine, two indole-mevalonate metabolites from *Claviceps paspali*. Tetrahedron Lett. 1980;21:231–4.
55. Munday-Finch SC, Wilkins AL, Miles CO. Isolation of paspaline B, an indole-diterpenoid from *Penicilium paxilli*. Phytochemistry. 1996;41:327–32.
56. Cole RJ, Kirksey JW, Wells JM. A new tremorgenic metabolite from *Penicillium paxilli*. Can J Microbiol. 1974;20:1159–62.
57. Springer JP, Clardy J, Wells JM, Cole RJ, Kirksey JW. The structure of paxilline, a tremorgenic metabolite of bainier. Tetrahedron Lett. 1975;16:2531–4.
58. Nozawa K, Horie Y, Udagawa S, Kawai K, Yamazaki M. Isolation of a new tremorgenic indologiterpene, 1′-O-acetylpaxilline, from *Emericella* striata and distribution of paxilline in *Emericella* spp. Chem Pharm Bull (Tokyo). 1989;37:1387–9.
59. Yamaguchi T, Nozawa K, Hosoe T, Nakajima S, Kawai K. Indoloditerpenes related to tremorgenic mycotoxins, penitrems, from *Penicillium crustosum*. Phytochemistry. 1993;32:1177–81.
60. Zhao LL. Search for new antineoplastic substances from marine-derived fungi. Dissertation, Fudan University, 2008.
61. Mantle PG, Weedon CM. Biosynthesis and transformation of tremorgenic indolediterpenoids by *Penicillium paxilli* and *Acremonium lolii*. Phytochemistry. 1994;36:1209–17.
62. Tomoda H, Tabata N, Yang DJ, Takayanagi H, Omura S. Terpendoles, novel ACAT inhibitors produced by *Albophoma yamanashiensis*. III. Production, isolation and structure elucidation of new components. J Antibiot. 1995;48:1–4.
63. Tarui Y, Chinen T, Nagumo Y, Motoyama T, Hayashi T, Hirota H, et al. Terpendole E and its derivative inhibit STLC- and GSK-1-resistant Eg5. ChemBioChem. 2014;15:934–8.
64. Xu LL, Pang XJ, Shi Q, Xian PJ, Tao YD, Yang XL. Two new prenylated indole diterpenoids from *Tolypocladium* sp. and their antimicrobial activities. Chem Biodivers. 2019;16: e1900116.
65. Belofsky GN, Gloer JB, Wicklow DT, Dowd PF. Antiinsectan alkaloids: shearinines A-C and a new paxilline derivative from the ascostromata of *Eupenicillium shearii*. Tetrahedron. 1995;51:3959–68.
66. Itabashi T, Hosoe T, Wakana D, Fukushima K, Takizawa K, Yaguchi T, et al. A new indoloditerpene derivative, penijanthine A, isolated from *Penicillium janthinellum*. J Nat Med. 2009;63:96–9.
67. Zhang YH, Huang SD, Pan HQ, Bian XQ, Wang ZY, Han AH, et al. Structure determination of two new indole-diterpenoids from *Penicillium* sp. CM-7 by NMR spectroscopy. Magn Reson Chem. 2014;52:306–9.

68. Gallagher RT, Finer J, Clardy J, Leutwiler A, Weibel FR, Acklin W, et al. Paspalinine, a tremorgenic metabolite from *Claviceps paspali* Stevens et Hall. Tetrahedron Lett. 1980;21:235–8.
69. Staub GM, Gloer KB, Gloer JB, Wicklow DT, Dowd PF. New paspalinine derivatives with antiinsectan activity from the sclerotia of *Aspergillus nomius*. Tetrahedron Lett. 1993;34:2569–72.
70. Huang XH, Nishida H, Tomoda H, Tabata N, Shiomi K, Yang DJ. Terpendoles, novel ACAT inhibitors produced by *Albophoma yamanashiensis*. II. Structure elucidation of terpendoles A, B, C and D. J Antibiot (Tokyo). 1995;48:5–11.
71. Gatenby WA, Munday-Finch SC, Wilkins AL, Miles CO. Terpendole M, a novel indole-diterpenoid isolated from *Lolium perenne* infected with the endophytic fungus *Neotyphodium lolii*. J Agric Food Chem. 1999;47:1092–7.
72. Junker B, Walker A, Connors N, Seeley A, Masurekar P, Hesse M. Production of indole diterpenes by *Aspergillus alliaceus*. Biotechnol Bioeng. 2006;95:919–37.
73. Liang JH, Huo XK, Cheng ZB, Sun CP, Zhao JC, Kang XH, et al. An indole diterpenoid isolated from the fungus *Drechmeria* sp. and its antimicrobial activity. Nat Prod Res. 2019;33:2770–6.
74. Valdes JJ, Cameron JE, Cole RJ. Aflatrem: a tremorgenic mycotoxin with acute neurotoxic effects. Environ Health Persp. 1985;62:459–63.
75. Gallagher RT, Wilson BJ. Aflatrem, the tremorgenic mycotoxin from *Aspergillus flavus*. Mycopathologia. 1979;66:183–5.
76. Cole RJ, Dorner JW, Lansden JA, Cox RH, Pape C, Cunfer B, et al. Paspalum staggers: isolation and identification of tremorgenic metabolites from sclerotia of *Claviceps paspali*. J Agric Food Chem. 1977;25:1197–201.
77. Uhlig S, Botha CJ, Vrålstad T, Rolén E, Miles CO. Indole-diterpenes and ergot alkaloids in *Cynodon dactylon* (bermuda grass) infected with *Claviceps cynodontis* from an outbreak of tremors in cattle. J Agric Food Chem. 2009;57:11112–9.
78. Alley MC, Scudiero DA, Monks A, Hursey ML, Czerwinski MJ, Fine DL, et al. Feasibility of drug screening with panels of human tumor cell lines using a microculture tetrazolium assay. Cancer Res. 1988;48:589–601.
79. DeFarias FP, Carvalho MF, Lee SH, Kaczorowski GJ, Suarez-Kurtz G. Effects of the $K^+$ channel blockers paspalitrem-C and paxilline on mammalian smooth muscle. Eur J Pharmacol. 1996;314:123–8.
80. Xu MJ, Gessner G, Groth I, Lange C, Christner A, Bruhn T, et al. Shearinines D-K, new indole triterpenoids from an endophytic *Penicillium* sp. (strain HKI0459) with blocking activity on large-conductance calcium-activated potassium channels. Tetrahedron. 2007;63:435–44.
81. Liu C, Noike M, Minami A, Oikawa H, Dairi T. Functional analysis of a prenyltransferase gene (paxD) in the paxilline biosynthetic gene cluster. Appl Microbiol Biot. 2014;98:199–206.
82. Liu C, Noike M, Minami A, Oikawa H, Dairi T. A fungal prenyltransferase catalyzes the regular diprenylation at positions 20 and 21 of paxilline. Biosci Biotech Bioch. 2014;78:448–54.
83. Ohshiro T, Morita H, Nur EAA, Hosoda K, Uchida R, Tomoda H. Voluhemins, new inhibitors of sterol O-acyltransferase, produced by *Volutella citrinella* BF-0440. J Antibiot (Tokyo). 2020;73:748–55.
84. Junko O, Arihiro T, Yoshiyuki T, Masaichi N, JPN. Patent JP2004168680, 18 Nov 2002.
85. Liu C, Minami A, Dairi T, Gomi K, Scott B, Oikawa H. Biosynthesis of shearinine: diversification of a tandem prenyl moiety of fungal indole diterpenes. Org Lett. 2016;18:5026–9.
86. Kudo K, Liu C, Matsumoto T, Minami A, Ozaki T, Toshima H, et al. Heterologous biosynthesis of fungal indole sesquiterpene sespendole. ChemBioChem. 2018;19:1492–7.
87. Jesus AE, Steyn PS, Heerden FR, Vleggaar R. Structure elucidation of the janthitrems, novel tremorgenic mycotoxins from *Penicillium janthinellum*. J Chem Soc Perkin Trans. 1984;1(15):697–701.
88. Wilkins AL, Miles CO, Ede RM, Gallagher RT, Munday SC. Structure elucidation of janthitrem B, a tremorgenic metabolite of *Penicillium janthinellum*, and relative configuration of the A and B rings of janthitrems B, E, and F. J Agric Food Chem. 1992;40:1307–9.
89. Penn J, Swift R, Wigley LJ, Mantle PG, Bilton JN, Sheppard RN. Janthitrems B and C, two principal indole-diterpenoids produced by *Penicillium janthinellum*. Phytochemistry. 1993;32:1431–4.
90. Smetanina OF, Kalinovsky AI, Khudyakova YV, Pivkin MV, Dmitrenok PS, Fedorov SN, et al. Indole alkaloids produced by a marine fungus isolate of *Penicillium janthinellum* Biourge. J Nat Prod. 2007;70:906–9.
91. Hennessy LM, Popay AJ, Finch SC, Clearwater MJ, Cave VM. Temperature and plant genotype alter alkaloid concentrations in ryegrass infected with an *Epichloë endophyte* and this affects an insect herbivore. Front Plant Sci. 2016;7:1097.
92. Ludlow EJ, Vassiliadis S, Ekanayake PN, Hettiarachchige IK, Reddy P, Sawbridge TI, et al. Analysis of the indole diterpene gene cluster for biosynthesis of the epoxy-janthitrems in *Epichloë endophytes*. Microorganisms. 2019;7:560.
93. Matsui C, Ikeda Y, Iinuma H, Kushida N, Kunisada T, Simizu S, et al. Isolation of a novel paxilline analog pyrapaxilline from fungus that inhibits LPS-induced NO production. J Antibiot (Tokyo). 2014;67:787–90.
94. Babu JV, Popay AJ, Miles CO, Wilkins AL, di Menna ME, Finch SC. Identification and structure elucidation of janthitrems A and D from *Penicillium janthinellum* and determination of the tremorgenic and anti-insect activity of janthitrems A and B. J Agric Food Chem. 2018;66:13116–25.
95. Gallagher RT, White EP, Mortimer PH. Ryegrass staggers: isolation of potent neurotoxins lolitrem A and lolitrem B from staggers-producing pastures. N Z Vet J. 1981;29:189–90.
96. Reddy P, Deseo MA, Ezernieks V, Guthridge K, Spangenberg G, Rochfort S. Toxic indole diterpenes from endophyte-infected perennial ryegrass *Lolium perenne* L.: isolation and stability. Toxins (Basel). 2019;11:16.
97. Miles CO, Munday SC, Wilkins AL, Ede RM, Towers NR. Large-scale isolation of lolitrem B and structure determination of lolitrem E. J Agric Food Chem. 1994;42:1488–92.
98. Imlach WL, Finch SC, Dunlop J, Dalziel JE. Structural determinants of lolitrems for inhibition of BK large conductance $Ca^{2+}$-activated $K^+$ channels. Eur J Pharmacol. 2009;605:36–45.
99. Munday-Finch SC, Wilkins AL, Miles CO, Ede RM, Thomason RA. Structure elucidation of lolitrem F, a naturally occurring stereoisomer of the tremorgenic mycotoxin lolitrem B, isolated from *Lolium perenne* infected with *Acremonium lolii*. J Agric Food Chem. 1996;44:2782–8.
100. Munday-Finch SC, Wilkins AL, Miles CO, Tomoda H, Omura S. Isolation and structure elucidation of lolilline, a possible biosynthetic precursor of the lolitrem family of tremorgenic mycotoxins. J Agric Food Chem. 1997;45:199–204.
101. Munday-Finch SC, Wilkins AL, Miles CO. Isolation of lolicine A, lolicine B, lolitriol, and lolitrem N from *Lolium perenne* infected with *Neotyphodium lolii* and evidence for the natural occurrence of 31-epilolitrem N and 31-epilolitrem F. J Agric Food Chem. 1998;46:590–8.
102. Laakso JA, Gloer JB, Wicklow DT, Dowd PF. A new penitrem analog with antiinsectan activity from the sclerotia of *Aspergillus sulphureus*. J Agric Food Chem. 1993;41:973–5.
103. Moldes-Anaya A, Rundberget T, Uhlig S, Rise F, Wilkins AL. Isolation and structure elucidation of secopenitrem D, an indole alkaloid from *Penicillium crustosum* Thom. Toxicon. 2011;57:259–65.


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